**Thrombolytics**

**Table A: Thrombolytics: Location, institution, ethics, animals, numbers**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study ID** | **Location** | **Institution** | **Ethics Statement** | **Animal** | **Number animals** |
| **26** | USA | Dept. Neurosurgery and Radiology, University of California | Performed in compliance with guidelines. Approved by Animal Review Committee. | Rabbits | 14 |
| **27** | USA | Yale University School of Medicine (Neurosurgery) | No | Rats | 15 |
| **28** | USA | Dept. Neurology, Cornell University Medical College | No | Rabbits | 43 |
| **30** | USA | Depts. Radiology, Neurology and Pathology, University of Massachusetts Medical school and Dept. Neurology at Worcester Memorial Hospital MA. | No | Rabbits | 26\* |
| **31** | USA | Dept. Neurosciences, University of California, san Diego School of Medicine | No | Rabbits | 408\* |
| **32** | USA | Dept. Neurology. George Washington University | No | Rabbits | 17 |
| **34** | USA | Depts. Neurology, Neuropathology and Neuroradiology, Veterans Administration Medical Centre and UCSD School of Medicine, San Diego | No | Rabbits | 140\* |
| **35** | USA | Depts. Radiology, neurology and pathology, university of Massachusetts medical school and Dept. Neurology at Worcester Memorial Hospital MA | No | Rabbits | 38\* |
| **33** | USA; Germany | Dept. Molecular and experimental medicine, Scripps Clinic and Research Foundation, La Jolla; Neurology Clinic, Heidelberg University | Performed in compliance with guidelines. Approved by Animal Review Committee. | Baboons | 30 |
| **37** | USA | Division of neurosurgery and Dept. Medical Biostatistics, university of Vermont | No | Rabbits | 17 |
| **38** | USA | Division of neurological surgery, Barrow Neurological institute, Phoenix | No | Rabbits | 61 |
| **39** | Japan | Daiichi Pharmaceuticals | No | Rats | Unknown\*\* |
| **40** | USA | Depts. neurology, veterans administration medical centre and UCSD School of medicine, San Diego | No | Rabbits | 186 |
| **41** | USA | Depts. Radiology, neurology and pathology, university of Massachusetts medical school; Dept. Neurology at Medical Centre of Central Massachusetts-Memorial, Worcester and Creative Biomolecules Inc. Mass | No | Rabbits | 24 |
| **42** | USA  USA | Dept. Neurology at Oregon Health Sciences University, Portland, Dept. Neurology at Marshfield Clinic Wis. And Dept. Neurosciences at UCSD, san Diego | Performed in compliance with guidelines. Approved by Animal Review Committee. | Rabbits | 90 |
| **43** | USA | Dept. Surgery, University of Arizona, Tucson | Approved by institutional Animal Care and Use Committee | Rabbits | 35 |
| **44** | Japan | Dept. Pharmacology and central laboratory for electron microscopy, Hamamatsu university school of medicine, Hamamatsu | No | Rats | 22\* |
| **45** | USA | Genentech Inc., San Fran, California; Dept. Neurosciences, University of California, San Diego | Approved by Genentech Animal Care and Use Committee | Rabbits | 156 |
| **46** | Japan | Dept. Pharmacology, Hammamatsu University School of Medicine, Hammamatsu | No | Rats | 46 |
| **47** | USA | Division of neurological surgery, Barrow Neurologial institute, Phoenix | Performed in compliance with guidelines. Approved by Animal Review Committee. | Rabbits | 30 |
| **48** | Japan | Sumitomo Pharmaceuticals | Performed in compliance with guidelines. | Rats | 555 |
| **49** | USA | Genentech Inc. San Fran and Dept. Neurosciences, University of California, San Diego | Approved by Genentech Animal Care and Use Committee | Rabbits | Unknown\*\* |
| **50** | Japan | Dept. Pharmacology, Hamamatu University School of Medicine, Hammamatsu | No | Rats | 76 |
| **51** | USA | Division of Neurosurgery (CEG, SJR, MMB), Vermont Center for Vascular Research, and Dept. of Medical Biostatistics (DBH), University of Vermont | Bilateral thoracotomies performed in accordance with procedures outlined by IACUC. (classified as ‘other’) | Rabbits | 68 |
| **52** | USA | Health Sciences Centers, Universities of Arizona and Oklahoma | No | Rabbits | 35 |
| **53** | USA | Dept. Neurosciences, University of California, San Diego; Dept. Cardiovascular Research, Genentech Inc. San Fran; College of Pharmacy, Wayne State University; Dept.s. Pharmacy & Neurology, Henry Ford Hospital, Detroit | Conducted in compliance with guidelines | Rabbits | 75 |
| **54** | France | Synthelabo Recherche | No | Rats | 71\* |
| **55** | Belgium | Center for Molecular & Vascular Biology, University of Leuven | Conducted according to guidelines | Rabbits | 62 |
| **56** | USA | Depts. Neurology, Neurosurgery, Radiology and Medicine, and Stanford Stroke Centre, Stanford University Medical Center | Approved by institutional animal panel on laboratory animal care | Rabbits | 40 |
| **58** | Germany | Max Plank Institute for Neurological Research, Dept. Experimental Neurology, Cologne | Performed 'in accordance with animal protection guidelines and approved by local authorities' | Rats | 16 |
| **126** | Germany | Max Plank Institute for Neurological Research, Dept. Experimental Neurology, Cologne | No | Rats | 17 |
| **125** | Germany | Max Plank Institute for Neurological Research, Dept. Experimental Neurology, Cologne, Dept. Radiology, University of Cologne Medical School | Performed 'in accordance with animal protection guidelines and approved by local authorities' | Rats | 20 |
| **59** | France | Sanofi Research, Toulouse | Approved by the Animal Care and Use Committee | Rats | 70 |
| **62** | USA | Cerebrovascular and neuroscience research Institute, Brigham and Women's Hospital/ Harvard medical School, Boston Massachusetts; Dept. pharmacology, University Medical Center at Stony Brook, new York. | No | Mice | 19 |
| **63** | USA | Dept. Neurology, Henry Ford health sciences Center, Detroit; Dept. of Physics, Oakland University, Rochester; Dept.. Biostatic and Research Epidemiology, Detroit. | Approved by the Care of Experimental Animals Committee | Rats | 60 |
| **127** | USA | Dept. Neurology, Henry Ford health sciences Center, Detroit; Dept. of Physics, Oakland University, Rochester; Dept.. Biostatic and Research Epidemiology, Detroit. | Approved by the Care of Experimental Animals Committee | Rats | 18 |
| **128** | USA | Dept. Neurology, Henry Ford health sciences Center, Detroit; Dept. of Physics, Oakland University, Rochester; Dept.. Biostatic and Research epidemiology, Detroit | Approved by the Care of Experimental Animals Committee | Rats | 24 |
| **64** | Germany | Max-Planck-Institute for Neurological Research, Cologne | Performed in accordance with guidelines and approved by the local authorities | Rats | 24 |
| **66** | USA | College of Pharmacy and Allied Health Professions, Wayne State University; Dept. Pharmacy Services and Neurology and Pathology, Henry Ford Hospital, Detroit | Approved by the Care of Experimental Animals Committee | Rats | 58 |
| **67** | France | Sanofi Research, Toulouse, | Approved by the Animal Care and Use Committee of Sanofi Recherche | Rats | 86 |
| **68** | Germany | Max Plank Institute | Procedures performed with ‘governmental approval’ according to guidelines | Mice | 17 |
| **69** | Canada | Foothills Hospital, Calgary, Alberta, Canada | No | Rats | 80 |
| **70** | USA | Divisions of neurosurgery and Surgical Research and Dept. Pharmacology, University of Vermont | They note that their method of euthanasia is the preferred method of their IACUC (counted as ‘other’) | Rabbits | 32 |
| **71** | USA; Japan | Neuroprotection research laboratory and Neurovascular Laboratory, Depts. Neurology and Radiology, Harvard medical school and Massachusetts General Hospital, Boston; Dept. Neurosurgery, Nihon University School of Medicine, Tokyo | Institutionally approved and conducted according to guidelines | Rats | 40 |
| **72** | USA | Henry Ford Hospital, Neurology Dept., Detroit | Approved by the Care of Experimental Animals Committee | Rats | 98 |
| **130** | USA | Dept. Neurology, Henry Ford Health Sciences Center, Detroit; Dept. Physics, Oakland University, Rochester, Mich. | Approved by the Care of Experimental Animals Committee | Rats | 72 |
| **73** | USA | Neuroprotection research laboratory, Depts. Neurology and Radiology, Massachusetts General Hospital; Harvard Medical School, Charlestown, And Program in Neuroscience, Harvard University, Boston | Performed according to an institutionally approved protocol and according to guidelines | Rats | 75 |
| **74** | USA | Division of Neurosurgery and Dept. Pharmacology and Totman Laboratory, University of Vermont; Dept. Biochemistry, University of Texas Southwestern Medical Center, Dallas; Dept. Pharmacology, New York Medical College, Valhalla | Performed with approval of institutional review board or animal care and use committee. | Rabbits | 69 |
| **75** | Germany; Canada; USA | Neurology University Clinic, Essen, Germany; Dept. Biomedical Engineering, Alberta university, Canada; Dept. Radiology, Stanford University, Stanford CA | Approved by institutional animal care committee | Rats | 15 |
| **77** | USA | Depts. Neurology, Biostatistics and epidemiology, Henry Ford Health Sciences Center, Detroit; Dept. Physics, Oakland University, Rochester, Michigan | Approved by the Care of Experimental Animals Committee | Rats | 33 |
| **78** | Germany | Dept. Experimental Neurology, Max Planck Institute for Neurological Research, Cologne | Conducted according to Guidelines and approved by the local government authorities | Mice | 10 |
| **79** | USA | Dept. Neuroscience, University of California at San Diego, La Jolla. | No | Rabbits | 131 |
| **80** | USA | Henry Ford Hospital, Detroit; Millennium Pharmaceuticals, Inc. Cambridge, MA | No | Rats | 44 |
| **81** | USA | Dept. Neurology, Henry Ford Hospital, Detroit; Dept. Physics, Oakland University, Rochester, Mich. | Approved by the Care of Experimental Animals Committee | Rats | 48 |
| **131** | USA; Japan | Neuroprotection research lab, Depts. Neurology and radiology, Harvard medical school, Massachusetts general hospital; Dept. Neurosurgery, Nihon University School of Medicine, Tokyo | No | Rats | 64\* |
| **82** | USA | Dept. of Neurosciences, University of California at San Diego School of Medicine; Dept. Neurology, Veterans Administration Medical Center, San Diego | Performed according to guidelines and approved by institutional animal care committee | Rabbits | 174\*\*\* |
| **83** | USA | Neuroprotection Research Laboratory, Depts. Radiology and Neurology; MGH-NMR Center, Dept. Radiology, Massachusetts General Hospital, Harvard Medical School, Mass. | Institutionally approved in accordance with guidelines | Rats | 28 |
| **84** | Germany | Dept. Neurology, Eberhard-Karls University, Tübingen | Performed according to guidelines and with approval of local government authorities | Mice | 84 |
| **85** | USA | Dept. of Neuroscience, University of California at San Diego, La Jolla | No | Rabbits | 165 |
| **86** | USA | Depts. Emergency Medicine , Neurology, and Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Detroit; Texas Biotechnology Corporation, Houston, Texas and Physics Dept., Oakland University, Rochester, Michigan | Approved by the Care of Experimental Animals Committee | Rats | 70\* |
| **87** | USA; Japan | Neuroprotection Research Laboratory, Depts. Neurology and Radiology, Massachusetts General Hospital, and Program in Neuroscience, Harvard Medical School; Dept. of neurosurgery, Kinki University School of Medicine, Osaka-Sayama, Japan; Yamanouchi pharmaceutical Co. Japan | Conducted under an institutionally approved protocol in accordance with guidelines | Rats | 44 |
| **89** | Japan | Dept. of Neurological Surgery, Nihon University School of Medicine, Tokyo | Approval by institutional Animal Care and Use Committee | Rats | 41 |
| **91** | USA | Dept. Neurology and Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit; Millennium Pharmaceuticals Inc. Cambridge, Mass; Dept. Physics, Oakland University, Rochester, Minnesota | Approval by institutional Animal Care and Use Committee | Rats | 56 |
| **92** | USA | Henry Ford Hospital, Detroit | No | Rats | 22 |
| **93** | USA | Neuroprotection Research Laboratory, Depts. of Radiology and Neurology, and Athinoula A. Martinos Center for Biomedical Imaging, Dept. of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachussets | Protocols institutionally approved in accordance with guidelines | Rats | 14 |
| **94** | Turkey | Dept. Neurosurgery Bas¸kent University, Faculty of Medicine Adana-Ankara; Dept. Neurosurgery Gazi University, Faculty of Medicine Ankara; Dept. Radiology Gazi University, Faculty of Medicine Ankara | Performed according to guidelines and approved by Institutional Animal Care and Use Committee | Rabbits | 28 |
| **95** | USA | Depts. Neurology and Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Detroit, Michigan; Dept. Physics, Oakland University, Rochester, Michigan; and Harper Hospital, MR Center, Detroit, Michigan | Approved by Institutional Animal Care and Use Committee | Rats | 46 |
| **96** | Japan | Fujisawa Pharmaceutical Co., Ltd., Kashima, Osaka, and Osaka Neurological Research Institute, Osaka | Performed according to guidelines  of the Laboratory Animal Experimental Committee of Fujisawa Pharmaceutical | Rats | 20\* |
| **97** | Japan | Second Dept. of Internal Medicine, Nippon Medical School, Tokyo | Performed according to guidelines and approved by local ethical committee | Rats | 15 |
| **98** | Germany | Dept. Experimental Neurology, Max-Planck Institute for Neurological Research, Cologne | Performed according to guidelines and approved by local authorities | Rats | 18 |
| **99** | Germany | Dept. Experimental Neurology, Max-Planck Institute for Neurological Research, Cologne | Performed according to guidelines and approved by local authorities | Rats | 31 |
| **100** | Canada; USA | Acute Stroke Program, Neurology Division, University of Alberta Hospital, Edmonton, Alberta, Canada; Centocor, Malvern, Pennsylvania | Approved by institutional Animal Welfare committee and performed according to guidelines | Rats | 54 |
| **101** | USA | GlaxoSmithKline, King of Prussia, Pennsylvania | Approved by institutional Animal Welfare and performed according to guidelines | Rats | 408\* |
| **103** | USA | Dept. Neurology, Henry Ford Health Sciences Center, Detroit; Dept. Vascular Biology, American Red Cross, Rockville; Dept. Neurology, Georgetown University Medical Center, Washington; Dept. Protein Development, Human Genome Sciences Inc. Rockville; and Dept. Physics, Oakland University, Rochester, Mich. | Approved by institutional Care of Experimental Animals Committee | Rats | 46 |
| **133** | USA | Dept. Neuroscience, University of California at San Diego, La Jolla; Veterans Affairs San Diego Healthcare System; and Veterans Medical Research Foundation, San Diego | Conducted according to institutional guidelines | Rabbits | 175 |
| **134** | USA | Dept. Neuroscience, University of California at San Diego; VA San Diego Healthcare System; and Veterans Medical Research Foundation, San Diego | Conducted according to institutional guidelines | Rabbits | 91 |
| **104** | France | Laboratoire de Pharmacologie, Faculté de Medecine, Lille | Conducted according to guidelines | Rats | 102 |
| **105** | Germany | Dept. Neurology, Ludwig Maximilians University, Munich | No | Rats | 24 |
| **106** | USA | University of California San Diego, Dept. Neuroscience, La Jolla; VASDHS and Veterans Medical Research Foundation, San Diego | Approved by institutional subcommittee on animal studies | Rabbits | 154\*\*\* |
| **107** | Japan | The Second Dept . Internal Medicine, Nippon Medical School, Tokyo, Japan; Pharmacology, Nippon Shinyaku, Kyoto | No | Rats | 39 |
| **108** | Japan | Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd. | No | Rats | 32\* |
| **109** | Japan | Dept. Neurological Surgery, Nihon University School of Medicine, Tokyo | Approved by institutional Animal care and Use Committee | Rats | 48\* |
| **110** | Canada; USA | Neurology Division, University of Alberta Hospital, Alberta, Canada; Efficacy Dept., MPI Research, Michigan | Approved by institutional Animal Welfare Committee and performed in according to guidelines. | Rats | 48 |
| **135** | USA | Depts. of Neurology, Emergency Medicine and Biostatistics and Research Epidemiology Henry Ford Health Sciences Center, Detroit, Mich; Laboratory of Blood and Vascular Biology, The Rockefeller University, New York, NY; Dept. Physics, Oakland University, Rochester, Mich. | Approved by institutional Care of Experimental Animals Committee | Rats | 62 |
| **136** | USA | Dept. Neurology and Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Detroit; Pfizer ClinSci CNS, Groton, Conn; Dept. Physics, Oakland University, Rochester, Michigan | Approved by institutional Care of Experimental Animals Committee | Rats | 88 |
| **112** | Germany; USA | Dept. Neurology, University of Heidelberg, Universitats Klinikum Mannheim, Theodor-Kutzer-Ufer Mannheim; stroke and Neurovascular Regulation Laboratory, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA; Institute Physiology and Pathology, University of Heidelberg, Theodor-Kutzer-Ufer Mannheim, Germany | No | Rats | 54 |
| **113** | USA | Dept. Neurology, Henry Ford Health Sciences Center, Detroit; Dept. Radiology, Henry Ford Health Sciences Center, MI; Dept. Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Detroit | Performed according to institutional guidelines under a protocol approved by the Institutional Animal Care and Use Committee | Rats | 18 |
| **114** | Germany  USA | Dept. Neurology, University of Heidelberg, Heidelberg, Germany; Stroke Branch, NINDS, NIH, Bethesda | Performed after approval by institutional animal care committee | Rats | 60 |
| **115** | USA | Dept. Neuroscience, University of California San Diego, La Jolla; VASDHS, San Diego; Veterans Medical Research Foundation, San Diego | Approved by institutional subcommittee on animal studies | Rabbits | 117\* |
| **116** | Japan | Fujisawa Pharmaceutical Co. Ltd. Kashima, Osaka | Performed under company guidelines | Guinea pigs | 120\* |
| **117** | Belgium; Japan | Center for Molecular and Vascular Biology, University of Leuven; Dept. Pharmacology, Hamamatsu University School of Medicine, Hamamatsu | Performed in compliance with guidelines and current institutional regulations for use and care of laboratory animals (guidelines) | Mice | 80\* |
| **119** | South Korea | National Creative Research Initiative Center for the Study of CNS Zinc. University of Ulsan College of Medicine, Seoul; Dept. Molecular Biology, Sejong University, Seoul | Performed in accordance with institutional Guidelines for Care and Use of Laboratory Animals | Rats | 92 |
| **120** | Japan | Dept. Neurology, Graduate School of Medicine and Dentistry, Okayama University, Japan; Dept. Neuropathology, Institute of Neurological sciences, Faculty of Medicine, Tottori University, Yonago, Japan; Dept.. Biochemistry, Kumamoto University school of Medicine, Japan | Approved by institutional Care of Experimental Animal Committee | Rats | 76 |
| **137** | USA | Dept. Neurology, Henry Ford Health Sciences Center, Detroit, Michigan; Dept. Physics, Oakland University, Rochester, Michigan | No | Rats | 59 |
| **121** | USA | Dept. Neurology, Henry Ford Health Sciences Center, Detroit | Performed according to institutional guidelines under a protocol approved by Institutional Animal Care and Use Committee | Rats | 22 |
| **123** | Switzerland | Dept. Neurology, University Hospital Zurich; Cardiovascular Research, Physiological Institute, University of Zurich | Performed according to guidelines and approved by local authorities | Mice | 36\* |
| **124** | Japan | Fujisawa Pharmaceutical Co, Ltd, Osaka | Performed under guidelines of the company Animal Experiment Committee | Squirrel monkeys | 33\* |
| **Total = 97**  **studies** | **USA 63; Japan 18; Germany 14; Canada 4; France 4; Belgium 2; South Korea 1; Turkey 1; Switzerland 1 (more than one country could work on a study)** | **Universities 45; hospitals 6; hospital and university collaboration 16; pharmaceutical company 9; pharmaceutical company and university and hospital collaboration 3; pharmaceutical and university collaboration 7; pharmaceutical and hospital collaboration 2; independent institute 7; independent institute and university 1; independent institute and pharmaceutical company 1** | **Nothing reported 30**  **Ethical statement reported 67 (performed according to guidelines 11; approved by local animal care and use committee 28; approved by committee and according to guidelines 26; other statements 2)** | **Rats 57 studies; rabbits 31 studies; mice 6 studies; guinea pigs 1 study; squirrel monkeys 1 study; baboons 1 study** | **6614\***  **Average no animals used per study 68** |

\*estimated (numbers poorly reported); \*\*could not estimate (poor reporting); \*\*\*at least, likely to be more

**Table B: Thrombolytics: Model, anaesthesia, conscious during embolization, how and when killed, what animals experienced**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Model** | **Anaesthesia for experimental procedures** (excluding anaesthesia prior to death) | **Conscious during embolisation** | **How killed** | **When killed (endpoint)** | **What animals experienced** |
| **26** | Rabbit cerebro-embolic stroke model | Yes |  | Fatal dose of pentobarbital | Not reported | Anaesthetised. Surgery to inject autologous clot into common carotid artery. Intravenous infusion of tpa / saline, angiograms performed, wounds closed, anaesthesia terminated. Animals were observed for 24 hours. Levels of consciousness, 'response to threat' ('loud noise', 'visual threat') and motor strength were recorded 24 hours after clot injection. Before being killed the rabbits brains were infused with blue or red dye for 3-5 minutes. |
| **27** | Rat model of ischemia | Yes |  | Saturated potassium chloride solution | Not reported | Anaesthetised lightly. Surgery to inject homologous clot into common carotid artery. Intravenous infusion of tpa / saline. Prior to death at 2 hours, blood withdrawn, dye injected intravenously, followed by potassium chloride solution. |
| **28** | Rabbit model of focal cerebral infarction | Yes |  | anaesthetised and decapitated | 29-33 hours after MCA occlusion | Anaesthetised. Surgery to occlude right common carotid artery and middle cerebral arteries, combined with 2 hours of Halothane-induced hypotension. Surgery involved exposing the right MCA transorbitally. Eye was removed, craniotomy was drilled. Eye orbit packed with sponge and eyelids sewn together. After 1.5 - 2 hours anaesthesia was discontinued and animals allowed to 'recover' for 24 hours. Treatment with heparin or thrombolytic agents commenced 24 hours after occlusion. They were then anaesthetised and killed (29-33 hours after occlusion). |
| **30** | Rabbit cerebro-embolisation model | Yes |  | 9 of the 14 animals died spontaneously 1 - 2 days post embolisation. The remaining animals killed by intracardiac injection of sodium pentobarbital/ lidocaine/ curare. | at intervals ranging from 5-13 days | Anaesthetised. Surgery to inject an autologous clot into the internal carotid artery. Angiographies, then treatment with saline or tpa fifteen minutes after embolization, then angiographies up to 3hrs. Presumably then anaesthesia stopped. 9 of the 14 animals died spontaneously 1-2 days post embolisation. The remaining animals were killed at intervals ranging from 5-13 days. |
| **31** | Rabbit small clot model, microsphere model, large clot model | Yes for large and small clot models: Microsphere model: details not given. |  | Some rabbits died of neurologic damage, some had their brains removed, some killed by carbon dioxide asphyxiation. | Surviving animals killed at 24 hours; at six days; one week; or at various times up to one week. | **Small clot model**: Anaesthetised. Surgery to place catheter. Animals allowed to recover for three hours. Clot injected without anaesthesia. Rabbits had TPA or saline intravenously. Some rabbits died prior to completion of tpa or saline treatment. After injection of clot and at 'various times thereafter' the neurologic function of each animal was rated as normal or abnormal (reduced levels of spontaneous activity, inability to stand, severely uncoordinated movements). Animals with 'gross behavioural disturbances' killed at 24 hours. Normally active animals maintained for 1 week and then killed. A separate set of animals were injected with small clots and TPA. These animals either died of the neurologic damage or were killed at various times up to one week post clot. In microsphere model a microsphere suspension was rapidly injected into the carotid artery. All animals that had not already died by 24 hours were killed. **Large clot model:** surgery to insert catheter into external carotid artery. Animals allowed 24 hours to recover. Animals were 'restrained briefly' and the clot was injected into the catheter followed by a saline flush. Animals were treated 30 mins or 4 hours later with saline or tpa. Surviving animals killed six days later. |
| **32** | Rabbit embolic stroke model | Yes |  | No information given. | No information given. | Surgery performed to place clots in the internal carotid artery. Angiography before and after embolisation and during treatment. Animals given tpa at 30 mins, 2 hrs and 4 hrs after embolisation. Angiograms conducted every 30 mins. Thoracotomies performed and animals were given an intracardiac dose of staining agent. Animals incubated at 38 degrees C. Then craniectomies performed and brains removed. |
| **34** | Rabbit modified embolic stroke model | Yes for catheterisation. Group 1 Yes; groups 2 and 3 did not have anaesthesia during embolisation. Groups 2 and 3 had local anaesthetic on ears for blood drawing | Yes | thiamylal sodium | 24, 32 or 48 hours after treatment | All rabbits anaesthetised for catheterisation and recovered for 3 hours. Only Group 1 re-anaesthetised for embolization. Groups 2 and 3 did not have anaesthesia during embolisation. Groups 2 and 3 had local anaesthetic on ears for blood drawing. Clots injected via catheter into middle cerebral artery. Group 1: reanaesthetised, angiogram, embolus, angiogram, treatment, angiogram X 3, death. Group 2: draw blood, embolus, draw blood, treatment after 8 hours, draw blood X 3, death. Group 3: draw blood, embolus, draw blood, treatment after 24 hours, draw blood X 2, death. Blood drawn by inserting catheter into central ear artery of awake animals, after anaesthetising central ear artery with lidocaine. Animals in groups 2 and 3 restrained. In unanaesthetised animals behavioural abnormalities could be observed within 30-50 seconds of injecting the clot.' (Neurological deficit was scored as mild if they exhibited 1 of following: nystagmus, circling or hemiparesis; or severe if they exhibited 2 of the above signs or seizure.) Endpoints: Group 1 = 24 hours after treatment, Group 2 = 32 hrs after treatment, Group3 = 48 hrs. |
| **35** | Rabbit cerebral embolic stroke model | Yes |  | Some died spontaneously, not told how others were killed | Killed electively' 3 - 14 days post stroke | Rabbits anaesthetised and surgery to inject clots into distal carotid internal artery. Angiographies. Then treatment or saline post embolisation and repeat angiographies up to 3hours. Unclear when anaesthesia terminated. Some animals died ‘spontaneously’ and others 'sacrificed electively' 3 - 14 days post embolisation. |
| **33** | Awake baboon model of acute middle cerebral artery stroke | Yes but seemingly only for the implantation of the right MCA Silastic inflatable balloon device | Yes | perfusion fixation | at 14 days | Anaesthesia given for implantation of the right MCA Silastic inflatable balloon device. After 3 hours of MCA occlusion and 30 mins of reperfusion (deflation of balloon) all baboons received 60 minute intravenous infusion of Rt-pa. Model called ‘awake baboon model’ so seems no anaesthesia during 3h occlusion procedure. Neurologic function measured using a neurologic scale (no details given). Serial CT scans performed after implantation of device, 24 hours and 10 days after occlusion. Animals killed at 14 days. |
| **37** | Rabbit model of thromboembolic stroke | Yes |  | sodium pentobarbital | At or before 4h | Rabbits anaesthetised. Surgery to drill into skull and place device to monitor intracranial pressure. Blood withdrawn for autologous clot. Clot injected into internal carotid artery. TPA initiated. Animals 'supported' for four hours after embolization, during which assessments regularly made. Rabbits killed at end of experiments (4hrs). Unclear if they emerged from anaesthesia during this period. |
| **38** | Rabbit model of embolic stroke using autologous arterial thrombus | Yes, for procedure to produce clot. 24 hours later anaesthetised again for embolisation. |  | intracardiac injection of saturated KCI | 6 h after embolisation | Rabbits anaesthetised. Auricular arteries of both ears damaged by scratching the vessel lumen to produce a thrombus. Rabbits allowed to recover and returned to their cages. 24 hours later re-anaesthetised, thrombus removed and surgery performed to achieve embolization (paralytic used). Treatment initiated 30 minutes after embolization and six hours after embolisation rabbits killed. Unclear if they emerged from anaesthesia during this period. |
| **39** | Rat cerebral thromboembolism model | Yes, to obtain blood for clots from carotid artery. Yes for surgery |  | Exsanguination under anaesthesia | Unclear: 'at certain times' after TPA given | Rats anesthetised and blood obtained from carotid artery for clot. At some point after rats re-anesthetised and surgery performed to achieve embolisation. Rats given rt-pa intravenously. 24 hours after embolisation the behaviour of each animal assessed and graded: 1. normal, 2. reduced spontaneous activity, 3. circumambulation and inclined body posture, 4. recumbency and stiffness of limbs, 5. dead. Some rats died before the experiment ended, others were killed at 'certain times' after tpa administration. |
| **40** | Rabbit model of embolic stroke using radiolabeled emboli | Nothing recorded |  | CO2 | 24 hrs after treatment | No details re anaesthesia. Catheter placed in extracranial carotid artery and a clot (made radioactive with iodine microspheres) advanced to the middle cerebral artery. Rabbits examined shortly after embolization: all had clinical signs of stroke: hemiparesis, circling or seizure. Rabbits treated with saline, tpa or streptokinase. All killed 24h after treatment. |
| **41** | Rabbit embolic stroke model | Yes |  | 18 rabbits died within 24 h of embolisation. 6 were killed with intracardiac injection of sodium pentothal/ lidocaine/ curare | Survivors killed 8 days after embolisation | Rabbits anaesthetised and surgery performed to produce embolization using an autologous clot. Angiographies performed. Treatment commenced 3hrs after embolization but unclear if animals still under anaesthetic. Repeated angiographies performed during 110 mins observation, unclear if animals awake or not. 18 rabbits died in the 24 hr period after embolisation. Rest killed at 2-8 days. |
| **42** | Rabbit model of embolic occlusion | Yes for catheterisation but seemingly not for embolisation | Yes | 52 animals died within 24 hours, survivors killed with intravenous 'Terminal' | Not reported | Rabbits anaesthetised for placement of catheter into internal carotid artery and allowed to recover (unclear how long for). Some given intravenous aspirin 18 h prior to embolization. Embolisation apparently not conducted under anaesthesia. Immediately after embolisation all animals showed signs of stroke: circling, hemiparesis, seizure. Rabbits given tpa and other agents up to 90 mins post embolization. Neurological function assessed 24h after stroke. 52 animals dead within 24 hours, rest killed, unclear when (24h?). |
| **43** | Rabbit model of cerebral ischaemia | yes for initial thrombus production procedure. Yes for surgery. |  | Not reported | 5 hours after treatment | Rabbits anaesthetised. Central arteries of the ear were damaged to produce a thrombus. Rabbits allowed to recover and returned to their cages. 2 days later rabbits re-anaesthetised, thrombus removed and surgery performed to inject thrombus into the internal carotid artery. Rabbits received tpa or other agents one or two hours after embolisation. Four rabbits had MRIs every 20 mins from embolisation until death. All rabbits were killed five hours after commencement of treatment. |
| **44** | Rat photothrombotic model of cerebral ischaemia | yes |  | overdose of pentobarbital | At 24 hours, 1 week and 8 weeks | Rats anaesthetised and had surgery to produce thrombus in middle cerebral artery using light and Rose Bengal, then given tpa. (Sham treatment group had surgery and light illumination but without rose Bengal. Animals were killed at 24 hours, 1 week and 8 weeks. Some animals died before endpoints of 1 and 8 weeks. |
| **45** | Rabbit model of embolic stroke | Yes, but also placed in restraining bags and stereotaxic frames. One group of rabbits had an artery and vein in ear catheterised whilst conscious. |  | Not reported | Not reported | Animals anaesthetised (hypnorm = sedation and analgesics), placed in restraining bags and stereotaxic frames. Surgery performed to flush labelled clots into cerebral circulation. Tpa or diluent administered. In 3 animals a hole drilled into skull, dura removed and a Doppler flow probe placed on brain surface. After embolisation some rabbits had two hours of imaging before being allowed to recover for 24 hours and then being killed. Others had an artery and a vein catheterised (whilst conscious) for blood sampling and drug administration, up to 120 mins after starting treatment. Time of death not known. |
| **46** | Rat middle cerebral artery thrombosis model | Yes for placement of catheter. |  | Some had brains removed under pentobarbital anaesthesia. Others anaesthetised then exsanguination | 24 hrs after completion of irradiation | Rats anaesthetised. Surgery performed to occlude middle cerebral artery using photo-illumination and Rose Bengal. Incisions closed after 90 mins observation. TPA administered intravenously after which the thrombus was observed for 60 mins with a microscope. 24 hrs after irradiation rats’ brains were removed under pentobarbital anaesthesia - animals not killed first. Presumably animals allowed to recover at some point before being killed at 24hrs. In a morphological study animals were killed by exsanguination, having first been anaesthetised with pentobarbital. |
| **47** | Rabbit model of embolic stroke using autologous arterial thrombus | Yes for procedure to produce thrombus. Yes for surgery |  | Overdose of intra-arterial KAX cocktail | Six hours after embolisation | Rabbits anaesthetised. The auricular arteries were damaged to produce a thrombus. Rabbits allowed to recover and returned to their cages. 24 hrs later rabbits re-anaesthetised, thrombus removed and surgery performed to inject thrombus into the internal carotid artery. Treatment initiated 30 minutes later, with intravenous / intra-arterial treatments lasting 2hrs. 6 hrs after embolisation rabbits were killed with an overdose of intra-arterial KAX cocktail. |
| **48** | Rat model of thromboembolic stroke | Yes for drawing blood from 'donor' rats. Yes for main procedure. |  | Some died. Manner of death for survivors not reported. | In one study at 48 hrs; in other study at 1, 3 or 6 hrs after drug infusion | Rats anaesthetised and had surgery to inject clot into common carotid artery. After embolisation facial twitching was observed in 'virtually all animals'. Tpa/ saline then administered. Most rats took food and water spontaneously after recovery from anaesthesia. Neurological function assessed 48h later: rats either normal, had forelimb flexion, circling, flexion of whole body, convulsion or coma, or were dead. At 48 hours all surviving rats were killed. |
| **49** | Rabbit model of embolic stroke | Yes. No for assessing bleeding from ears by ‘shaving’ ears |  | Not reported. | After 26 hours | Rabbits anaesthetised and surgery performed to inject radioactive clots into the carotid artery. Tpa then administered. Some animals had blood samples taken at regular intervals up to 2hr post treatment. Rabbits had 2hrs of imaging. They were then allowed to recover for a period of 24 hours before being killed. |
| **50** | Rat MCA thrombosis model using green light and rose bengal | Yes, and local anaesthetic to wound (caused by craniotomy) |  | brains removed under anaesthesia | 24 hours after irradiation | Rats anaesthetised and surgery conducted to perform a sub temporal craniotomy and irradiate and thrombotically occlude the middle cerebral artery, using Rose Bengal. 30 minutes after occlusion thrombolytic agents were administered. After 90 mins observation incision closed. Local anaesthetic applied to wound every 3 hrs until animal killed. 24 hrs after irradiation rats killed. |
| **51** | Rabbit model of thromboembolic stroke | Yes |  | overdose of sodium pentobarbital | At end of experiment, at 10-12 hours | Rabbits anaesthetised and surgery conducted to perform bilateral craniectomies, for placement of electrodes, monitors and sensors. An autologous clot was injected into the carotid artery. Rabbits were x-rayed and given intravenous t-PA / saline solution 3, 4, or 5 hours after embolization, with experiments finishing 4 hours after treatment, at which point rabbits were killed. Radiographs were obtained three times during the experimental period. 4 animals had ‘early deaths’. |
| **52** | Rabbit model of embolic stroke | Yes for thrombus production. Yes for main procedure |  | Not reported | four hours after treatment | Rabbits anaesthetised. Auricular arteries damaged to produce thrombus. Returned to cages for 2 days then re-anaesthetised and surgery performed to harvest thrombus and inject it into the internal carotid artery. Halothane discontinued. 2nd dose of 'tranquillising mixture' given, and repeated at 60 min intervals. Treatment administered 2hrs post embolisation. Rabbits killed 4 hrs after treatment. |
| **53** | Rabbit model of MCA embolism | Yes for catheterisation but not for embolisation (apart from a sub group) | Yes | Beuthanasia-D. | At 18 hours | Rabbits anaesthetised for catheter insertion. Catheter accessible outside the animal's neck. Incision closed, animals allowed to recover for 3hrs, after which they were restrained (not told how) and clot injected into middle cerebral artery via protruding catheter. Sub group anaesthetised with halothane to explore its effect on BP. 18 hours after embolisation animals evaluated for neurological function or death. Abnormal animals had greatly reduced levels of spontaneous activity, inability to stand, uncoordinated movements. Animals killed after evaluation, at 18hrs. |
| **54** | Rat thromboembolic stroke model | Yes for donor rats to obtain blood for the clots. Yes for embolisation and three hours after |  | Overdose of pentobarbital. | At 24 hours | Rats anaesthetised and surgery performed to inject clot into internal carotid artery. Drugs administered post embolisation and animals maintained under anaesthesia for 3 hrs. Some anaesthetised rats had drugs without embolization. 24 hours after embolisation rats assessed neurologically; this included being held upside down by tail and scored according to whether there was flexion of forelimb to the contralateral side. Rats killed after assessment. |
| **55** | Rabbit embolic stroke model | yes |  | Not reported | At 5 hours | Rabbits pre-medicated and cannula inserted into right marginal ear vein for maintenance anaesthesia and drug infusions. Rabbits anaesthetised and surgery performed to inject clots into internal carotid artery. 15 mins after embolization, infusions started. Rabbits observed for 75 mins, wounds closed and rabbits allowed to recover from anaesthesia. 5 hrs after embolization rabbits scored neurologically, assessing hemiparesis, persistent stupor, circling behaviour. Some died within 5 hr period. After scoring animals were killed. |
| **56** | Rabbit model of embolic stroke, using MRI | Yes |  | barbiturate overdose | Six hours after embolisation | Rabbits anaesthetised and surgery performed to inject embolus into the cerebral circulation. Animals then transferred to MRI scanner and scanned within 30 mins of embolization, then at 2, 3 & 5hrs post embolization, with each scan taking 20-30 mins. Drugs given intravenously 60 mins post embolisation via ear vein. 4 rabbits not given drugs (or embolus?). 6 hrs after embolisation rabbits killed. Was anaesthesia maintained during scans? |
| **58** | Rat model of embolic stroke | Yes |  | frozen in liquid nitrogen | 3 hours after embolisation | Rats anaesthetised and surgery performed to inject clots into the carotid artery. Treated animals had TPA infused 15 minutes after embolisation over 45 minute period. Animals restrained in a stereotaxic head-holder for MRI scanning. Cerebral blood flow measured 3 hrs after embolisation. Tracer infused intravenously over 60 seconds, blood samples collected repeatedly using filter paper. 3 hours after embolisation all animals killed. |
| **126** | Rat model of thromboembolic stroke | No information given |  | Not reported | At 3.5 hours | Rats had surgery for intracarotid injection of autologous clots. No information given on surgical technique or anaesthesia. Rats had either tpa or saline over a period of 45 minutes, 15 minutes after embolisation. Rats had MRI scans, unclear how many. Experiment finished 3.5 hrs after embolisation. |
| **125** | Validation of an 'improved' rat model of thromboembolic stroke | Yes |  | One group killed with injection of potassium. Another group killed by having heads frozen in liquid nitrogen | 3 hours after embolisation | Rats anaesthetised and surgery performed to achieve embolisation by injecting clots into carotid artery. Animals had intracarotid infusion of tpa or saline 15 minutes after embolization, continuing for 45 mins. In another group, regional cerebral blood flow was measured by autoradiography using a 'tracer' infused intravenously. Rats killed 3 hrs after embolization. |
| **59** | Thrombo-embolic rat model of cerebral ischaemia | Yes |  | anaesthetised then killed by perfusion fixation | 24 hours after embolisation | Autologous clots were formed from arterial blood which was withdrawn into a syringe approximately 2 hours before main procedure. Animals anaesthetised and surgery performed to inject clot into right external carotid artery. 1hr after embolisation animals had tpa, saline or other agent administered over 45 mins. Wounds closed and anaesthesia reversed 2hrs after stroke. Neurological status of surviving rats evaluated 3 hours post embolisation, involving being held upside down by the tail, resistance to lateral push. Post embolisation animals lethargic and showed asymmetric posture with flexion of the contralateral forelimb. Rats also had their tails cut to observe bleeding times. Rats were killed 24 hours after embolisation. 22 rats died before 24 hrs. |
| **62** | GM mouse models of ischaemia using intraluminal filament | Yes |  | Not reported | 24 hours after | Mice anaesthetised and surgery performed to placing a probe on the brain and to introduce a filament into middle cerebral artery to produce transient ischaemia. After 2-3 hours of occlusion filament withdrawn to allow reperfusion. TPA administered intravenously. Regional cerebral blood flow monitored using laser Doppler flowmetry. Animals killed 24 hours after onset of ischaemia. |
| **63** | Newly developed rat cerebral embolic model | Yes |  | anaesthetised then transcardially perfused | 24 hours or 7 days after embolization | Rats anaesthetised and surgery performed to occlude middle cerebral artery with embolus. 1 hr after embolisation rats had tpa, vehicle or saline infused intravenously over 30 mins. Neurological examinations performed 1 hr, 1 day and 7 days after embolisation. Animals killed either 24 h or 7 days after embolization. |
| **127** | Newly developed model of rat cerebral artery thrombotic stroke | Yes, and during MRI scanning. |  | anaesthetised then transcardially perfused | 2 died 4-5 hours after embolization, the rest were killed at one week, or at 4-5 hours | Rats anaesthetised, blood withdrawn for autologous clot and surgery performed to inject clot into internal carotid artery. Some animals untreated, others had tpa 2 hrs after embolization, infused over 30 mins. After embolisation animals were scanned, during which anaesthesia maintained. Stereotaxic ear bars used to minimise movement during scanning. Scans performed 'pre-ischaemia' and 'repeatedly for 4-5 hours after embolisation, then at 1, 2 & 7 days, each sequence taking 16 mins. 2 rats died 4-5 hours after embolization, 4 animals were killed at 4-5 hours and 12 at 1 week. |
| **128** | Reproducible rat model of embolic stroke | Yes |  | anaesthetised then transcardially perfused | 5 hours or 1 wk after embolisation | Rats anaesthetised and surgery performed to inject clot into internal carotid artery. Some rats untreated, others given tpa intravenously 1 hour after embolisation over 30 mins. After embolisation animals scanned, during which anaesthesia maintained. Stereotaxic ear bars used to minimise movement. Scans were performed 'pre-ischaemia', then 'repeatedly for 4-5 hours after embolisation, then at 1,2 and 7 days, each sequence taking 16 mins. 5 animals died in the period 4-24 hours post embolization, 7 killed 5 hours after embolisation and 12 at one week. |
| **64** | Rat model of focal cerebral ischaemia | Yes |  | Not reported | Not reported | Rats anaesthetised and surgery performed to inject clots into the internal carotid artery. Animals fixed in stereotactic head holder and placed in scanner. Treated animals had intracarotid tpa or saline infusion 1.5, 3 or 4.5 h after embolism, continuing for 1 hr. MRI scans conducted 8h after embolism (untreated rats), 5h after thrombolysis initiated (treated rats). Time of death unreported. |
| **66** | Adaptation of a rat model of acute Middle Cerebral Artery Occlusion | Yes |  | Under general anaesthesia animals were transcardially perfused | 18-24 hours after MCA occlusion | Rats anaesthetised and surgery performed to produce blockage at origin of MCA using intraluminal filament. Animals allowed to recover from anaesthesia. Received tpa or saline intravenously over 20 mins, beginning 5 mins before reperfusion. Reperfusion performed at various times between 1h and 24 h by withdrawing filament. One rat died immediately after MCA reopened. Animals returned to cages until 18-24 hrs post MCA occlusion, then neurologically assessed and killed. |
| **67** | Thrombo-embolic rat MCAO model | Yes |  | perfusion fixation | some died, others killed at 24h and 48h | Rats anaesthetised and surgery performed to inject clot into carotid artery. Control animals had sham surgery but no clots. Angiography performed before and after embolisation, then wounds closed and anaesthesia reversed. Neurological examinations conducted 3h after embolization, which involved being held upside down by the tail, pushed to test resistance. Post embolisation animals were lethargic and often showed asymmetric posture with flexion of contralateral forelimb. Animals that survived were killed at 24h post embolization (9 died before). [Some rats placed in head holder for MRI experiments. Some had tpa without embolization, with bleeding time determined by tail transection at end of 45 min infusion. Time of death unclear for these rats.] |
| **68** | Mouse model of middle cerebral artery occlusion | Yes |  | anaesthetised and decapitated | 24 h after occlusion | Mice anaesthetised and surgery performed to fix a probe to the skull and to produce focal cerebral ischaemia by transient thread occlusion of MCA for 90 mins. 15 mins after onset of occlusion animals received intravenous tpa, water or nothing. Reperfusion initiated by withdrawal of the thread, cerebral blood flow measured. 30 mins later anaesthesia stopped and animals returned to cages. 1 mouse died in 24 h post-occlusion period. 24 hrs after occlusion mice assessed neurologically and then killed. |
| **69** | Rat models of i. global and ii. focal ischemia | Global ischaemia: yes  Focal ischaemia: Yes for surgery but anaesthesia stopped during induction of ischaemia |  | Global ischaemia: anesthetized and transcardiac perfusion. Focal ischaemia: anesthetized and decapitated | Global: At 7 days  Focal: at 24 hours | **Global ischaemia:** Rats anaesthetised and surgery performed to place ligatures around carotid arteries and para-vertebral musculature. Wounds closed and animals returned to cages overnight. Next day rats subjected to 10 mins severe ischemia by tightening ligatures (think this under anaesthesia). Unresponsive rats were reperfused. Then given saline or tpa. Killed at 7 days. **Focal ischaemia:** rats anaesthetised and surgery performed to ligate the carotid artery and drill holes in skull to place probe. Rats subjected to 30, 60, or 120 mins of ischemia, during which rats allowed to regain consciousness. At end of ischemic period rats briefly reanesthetized for removal of a clip that had been placed on the MCA. Rats then given tpa. Killed at 24 hrs. |
| **70** | Rabbit model of thromboembolic stroke | Yes |  | exsanguination and subsequent bilateral thoracotomies | 2 hours after treatment | Rabbits given intravenous cobra venom factor. 48h later anaesthetised and surgery performed to drill troughs in skull for monitoring of CBF etc. and to inject clot into the carotid artery. Wounds were repaired and a radiograph taken of the head and neck. 3 hours after embolisation animals had tpa or saline and supported for 2h following treatment, then killed. |
| **71** | Embolic versus mechanical models of focal cerebral ischaemia in rats | Yes |  | overdose of sodium pentobarbital | At 24h | Rats anaesthetised and surgery performed to produce ischaemia either by injecting a clot into the cerebral circulation, by advancing a monofilament suture up the ICA and withdrawing it after 2h to allow reperfusion, or by advancing a suture and not withdrawing it (global ischaemia). 2h after occlusion rats had tpa or saline intravenously infused over 30 mins, except those with global ischaemia. They had CT scans 30 & 60 mins after occlusion, with heads in 'custom made head holder', anaesthesia maintained. All rats allowed to recover in individual cages, then killed at 24h. |
| **72** | Rat model of MCAO | Yes |  | Anesthetized then perfused transcardially | At 2 days and 7 days | Rats anaesthetised and surgery performed to inject the clot into the ICA. Neurologic examinations performed at 2h, 4h, 2 days and 7 days after clot injection. All animals exhibited severe neurologic deficits after embolization and before intervention. Rats had tpa or other agents and were killed at either 2 days or 7 days. Some died within 24 hours after embolization. |
| **130** | Rat model of cerebral embolic ischaemia | Yes |  | anesthetized and perfused transcardially | At 6h or 24h post stroke, or by 48h post embolisation | Rats anaesthetised and surgery performed to occlude MCA by placement of a clot at its origin. Tpa infused intravenously over 30 mins at either 1 or 4h post stroke. Some rats also had antibody infused over 3 mins, some rats completely untreated. Rats tested for neurological function at 4h and 2 days after stroke. Severe neurological deficit was evident in all groups at 4h post stroke. 2 rats died within 24 h from brain oedema. Rats killed at 6h, 1 day or 2 days after stroke. |
| **73** | 2 rat models: embolic model using homologous clot; mechanical model using filament | yes |  | lethal dose of sodium pentobarbital and transcardially perfused | at 24h | Rats anaesthetised and surgery performed to occlude internal carotid arteries using either a clot or a filament. Reperfusion was achieved at 6h post stroke by either withdrawing the filament, or by intravenous administration of tpa over 30 mins (for the clot), or both tpa and filament withdrawal. Unclear how long anaesthesia maintained. At 24h rats assessed neurologically, then killed. |
| **74** | Rabbit model of thromboembolic stroke | yes |  | exsanguination via the arterial line and subsequent bilateral thoracotomies | 7 h after embolisation | Rabbits anaesthetised and surgery performed on skull to place electrodes and monitors and to inject clot into carotid artery. tpa or saline administered over 2hrs continuous infusion, from 3-5 h after embolisation. Each animal 'supported' for 2h after tpa infusion. 7h after embolisation rabbits killed. 1 died before 7hrs. Unclear how long anaesthesia maintained. |
| **75** | Rat model of thrombo-embolic stroke | Yes |  | Page 422 missing | Page 422 missing | Rats anaesthetised and surgery performed to inject 15 small clots into ICA. Rats had x-ray angiographies post embolization and at 6hrs. Rats also had MRI scans. All had intracarotid infusion of tpa or saline over 90 minutes, starting 1hour post-stroke. Experiment ended 6hrs. Method/ time of death unclear (assume 6hrs). |
| **77** | Rat model of embolic stroke | yes |  | decapitated | 4-5 h post-embolisation | Rats anaesthetised and surgery performed to inject clot into ICA to occlude the MCA and cause stroke. Rats had tpa either 1 or 4hrs post embolism, or some untreated. Rats had MRI scans before embolisation and repeatedly after embolisation for 4-5 hours or for 7 hours. Scans also performed at 1, 2 and 7 days post embolisation. Anaesthesia during scans and stereotaxic ear bars used to minimise movement. Time of death unclear but presumably 1,2, 7 days post stroke. |
| **78** | Mouse model of cerebral thrombo-embolism | Yes |  | Anaesthetised then decapitated | At 24 h | Mice anaesthetised and surgery performed to inject clots into the ICA and to attach probes to skull. Treated mice had tpa infused over 45 mins, 15 mins after embolisation. 2h post embolisation anaesthesia was stopped and animals returned to their cages. Neurological functioning tested at 24h. Severe neurological deficits revealed. Animals presumably killed at 24h, after neuro testing. |
| **79** | Rabbit model of MCA occlusion | Yes for catheterisation but not embolisation | Yes | Not reported | 48 h after embolisation | Rabbits anaesthetised and surgery performed to place a catheter into carotid artery so that it was accessible outside. Animals allowed to recover from anaesthesia for at least 2h prior to embolization, which achieved by injecting clot into catheter while animals awake and restrained. If the rabbit did not react to initial clot (e.g. with nystagmus\*, hemiparesis, seizure), further clots were injected until they did. Rabbits had tpa, another agent, both or vehicle, unclear when/ how. Catheter then ligated close to the neck and rest of catheter cut off. So rabbits had some catheter remaining in their necks. Some animals died before 48h, when rest killed. |
| **80** | Rat model of thrombo-embolic stroke | No information given (poster) |  | Not reported | 7 days after MCA occlusion | Rats were subjected to MCA occlusion then given an agent, or agent plus tpa infused intravenously at 2 h, 4 h, or 6 h after MCA occlusion. Controls had saline at 2 h after MCAO. Rats killed 7 days after MCAO. (Poster, with little detail) |
| **81** | Unanaesthetised rat model of focal cerebral embolic ischaemia | yes for surgery but not for clot injection, (anaesthesia found to reduce cerebral blood flow). | Yes | anaesthetised and transcardially perfused | 48 h after ischaemia | Rats anaesthetised and surgery performed to place a catheter and take blood for clot. Animals allowed to recover for 45 mins, then clot injected into origin of MCA while rats awake. Neurological examinations conducted immediately, 4 and 48 h after clot injection. Rats had 30 min infusion tpa at 2h or 4h. Animals observed to turn or circle to left immediately after clot injection. Moderate / severe neurological deficit persisted at 48h for rats without tpa. MRI scans performed on 3 sham operated rats. Stereotaxic ear bars used and anaesthesia continued at maintenance levels. |
| **131** | Rat thromboembolic stroke model | yes |  | Not reported | 24h after injection of emboli | Rats anaesthetised and surgery performed to place a catheter in the femoral artery to monitor blood pressure and heart rate. Some rats had probes placed over frontoparietal cortex. Multiple micro-emboli were injected into the ICA. Immediately after injection all rats showed detectable neurological deficits. Animals reanaesthetised (for catheterisation of femoral vein) and tpa or saline infused over 30 mins, 2 or 6h after embolization. Rats killed at 24h post embolization. |
| **82** | Rabbit embolic stroke model | yes for insertion of catheter but not embolisation | Yes | Beuthansia-D (Pentobarbital Sodium and Phenytoin Sodium) | 48 hours after embolization | Rabbits anaesthetised for insertion of catheter into carotid artery, with distal end left accessible. Animals recovered from anaesthesia for at least 2 hours before embolization, which was achieved by injecting clot via catheter (presumably whilst rabbits awake). If rabbit did not react (nystagmus,  hemiparesis, uncoordinated movements) within 3 mins, another clot injected. Then catheter ligated close to the skin and rest cut off. 1h post embolization rabbits given tpa, another agent or vehicle. Some rabbits had agents but not surgery/ embolism. Animals killed at 48h, some died prior. |
| **83** | Rat embolic stroke model | yes |  | lethal overdose of sodium pentobarbital then transcardially perfused | at about 9 h and 24 h | Rats anaesthetised and surgery conducted to inject clot into carotid artery via catheter. Rats also had hole drilled in skulls to place probe. Regional blood flow was measured before and up to 30 mins after MCAO. Animals then allowed to recover, unclear how long for. Then re-anaesthetised, catheterised X 3, tracheotomised and immobilized for MRIs. MRIs performed from 2 h before, until up to 3 h or 24h after drug administration. 6h after MCA occlusion tpa or saline intravenously administered. Unclear how long anaesthesia maintained. Animals killed after MRIs. |
| **84** | Mouse model of focal ischaemia using intraluminal thread | Yes |  | decapitated, some with and some without anaesthesia | Twenty-four hours after MCA occlusion | Mice anaesthetised and surgery performed to induce focal cerebral ischemia by occluding the MCA with an intraluminal filament, to catheterise mouse and to attach probe to skull. Immediately after occlusion or 90 mins after, mice had intravenous infusion of saline, heparin or tpa at various doses. Controls had agents but no occlusion. Mice having agents immediately after MCAO had anaesthesia discontinued, x-rays 2hrs later, with intraperitoneal injection of ?radioactive agent, then killed. The rest of the mice were reanaesthetised 24h after MCAO and killed. |
| **85** | Rabbit model of thrombo-embolic stroke | Not recorded (nothing reported but clear that animals awake during embolization) | Yes | Not reported | 48 hours after embolization | Anaesthesia not reported but presumably done for catheterisation but not embolisation. Carotid artery catheterised and emboli injected. If the animal did not react to embolization, a second blood clot was injected. Most responded with nystagmus, pupillary dilation, hemiparesis, seizure, or brief uncoordinated jerking movements. After embolization catheter ligated close to the neck and rest of the catheter cut off. Tpa and/ or agents administered by infusion over 30 mins. Some rabbits died before experiment completed. Surviving rabbits killed at 48h. |
| **86** | Rat model of embolic stroke | yes |  | anesthetized and killed, manner not reported. | Two days after MCA occlusion | Rats anaesthetised and surgery performed to place a clot at the origin of the MCA via a catheter. Rats had various doses of agent or saline infused immediately after MCAO, over 48 h, or agent, tpa or combination of both infused 4 h or 6h after MCAO; tPA over 30 minutes and other agent over 44h. Rats killed at 48h. |
| **87** | Rat model of embolic stroke | yes |  | deeply anesthetized and decapitated | Twenty-four hours after clot injection | Rats anaesthetised and surgery performed to inject clot into middle cerebral artery via catheter, also surgery to place probes to measure rcbf. 1h later tpa and other agents administered. Neurological examinations performed 24h after clot injection, then rats killed. |
| **89** | Rat model of thromboembolic stroke | yes |  | overdose of sodium pentobarbital | At 24 hours after embolisation | Rats anaesthetised and surgery performed to inject clots into the ICA. tPA administered at 2h or 6 h after embolisation. Animals reanesthetized (not clear after how long), femoral vein catheterized and tPA infused over 30 mins. Untreated controls had saline administered at 2h. In another experiment hydralazine was dissolved in drinking water given daily to rats for 1 week prior to ischemia. Surgery to induce embolic ischemia and to place probes was performed and then either saline at 2h, or tPA at 6h was administered. Rats killed at 24h. |
| **91** | Rat model of embolic focal cerebral ischaemia | yes |  | anaesthetised and killed, manner not reported. | at 7 days after MCA occlusion | Rats anaesthetised and surgery performed to occlude MCA by placement of a clot at origin of MCA, using a catheter. After embolization, animals had intravenous infusions of agent or tpa plus agent at 2, 4 or 6h, or tpa at 2 or 4h, or saline at 2h. 1h after MCA occlusion, all rats exhibited neurological deficits. Neurological assessments at 1, 2, and 7 days after MCAO. Rats killed at 7 days. |
| **92** | Rat model of focal cerebral embolic ischemia | Not reported |  | Not reported | 28 days after ischemia | No info re anaesthesia. (This is a poster, so little detail.) Rats subjected to MCAO using a single clot. TNK-tPA administered intra-arterially via an internal carotid catheter at 2, 4 or 6h after occlusion. Non-treated ischemic rats used as controls. Neurological function assessed using 1. Rotarod test, 2. Adhesive-removal test and 3. Footfault test.\*\* All rats killed 28 days after ischemia. |
| **93** | Rat embolic stroke model | yes |  | lethal overdose of sodium pentobarbital and transcardially perfused | 8 hours after embolisation | Rats anaesthetised and surgery performed to inject clot into carotid artery. For MRI scanning rats tracheotomised, mechanically ventilated and catheterized. 6h after MCAO, saline or tPA infused intravenously over 20 mins. Contrast agent injected. MRI scans done before, after and during tPA / saline administration. All saline treated rats and some tpa treated rats were injected with another agent during MRIs. Rats killed after MRI experiments (approx 8 h after ischemia). |
| **94** | Rabbit Model of Acute Thromboembolic Stroke | yes |  | thiopental overdose | Not reported | Rabbits anaesthetised and surgery performed to place clot into common carotid artery. Occlusion checked by serial angiograms using injections of contrast agent. Rabbits had intravenous t-PA or saline, local intra-arterial t-PA or saline, 30 minutes after embolization, infused over 28 mins. Then angiograms performed every 15 mins, up to 3h after treatment initiation. Rabbits’ neurologic status evaluated during angiography (how?). All rabbits killed at end of experiment. |
| **95** | Rat model of embolic stroke | Yes and during MRI measurements |  | Anesthetized and transcardially perfused | At 2 days or 7 days | Rats anaesthetised (presumably, not reported) and surgery performed to inject a clot into the internal carotid artery to block the middle cerebral artery. Some animals had no treatment. Others had t-PA 1h, 4h or 6h post MCAO. During MRI scanning anaesthesia maintained and stereotaxic ear bars used to minimize movement. MRIs performed before ischemia, then repeatedly for 4-5 hrs or 7 or 8 hrs post embolization, and at 1, 2 and 7 days, each sequence taking approx. 34 mins. Some rats killed at 2 days but most after final MRI, at 7 days. 1 rat died shortly after embolization. |
| **96** | Rat model thrombotic focal cerebral ischaemia using Rose Bengal/ green light | yes |  | Not reported | 24 hours after MCA occlusion | Rats anaesthetised and surgery conducted to perform a sub-temporal craniotomy, to place a laser-Doppler probe on the dura mater and to induce ischemia photochemically with green light and intravenous Rose-bengal. After wound closure rats returned to their cages. Saline, tacrolimus or tpa administered intravenously immediately after MCA occlusion. Rats killed 24h after MCAO. |
| **97** | Rat model of embolic stroke | Yes for main experiment |  | overdose of pentobarbital | 24 hours after embolisation | 1 day before main experiment some rats had a hole drilled in their skulls for placement of laser doppler probe and a tube fixed onto skull around hole (presumably under anaesthesia, not mentioned). Next day all rats anaesthetised and had surgery to induce ischemia by flushing clots into carotid artery via catheter. Some rats had MRI scans 1h after embolization (no details given) with contrast agent via femoral vein. Rats that had probe placed had monteplase or saline 30 mins after embolization and rcbf measured. Rats killed 24h post embolization. |
| **98** | Rat model of MCA clot embolism | yes |  | Anesthetized and transcardially fixed by perfusion | day 3 after embolization | Rats anaesthetised and surgery performed to embolise MCA by inserting catheter into internal carotid artery and injecting clots. MRI scans performed 2-3 hrs after embolism. (No details re how animals immobilised etc.) 3 hrs after embolization animals received intracarotid injection of tPA or saline, after MRI scans done. After treatment catheter was removed, wounds closed and animals allowed to recover from anaesthesia. Rats killed on day 3, some died before this point. |
| **99** | Rat model of thromboembolic stroke | yes |  | Brains frozen in situ | 7 hours after embolism | Rats anaesthetised and surgery performed to induce stroke by injecting clots into the carotid circulation, via a catheter. Embolisation was performed inside an MRI scanner, with rats’ heads immobilised in a stereotaxic head holder. 1 hr after embolism, animals given either saline, intra-arterial, or intravenous tPA infusions. MRI scans were obtained before embolism and at 1, 2, and 6h after embolism. Unclear how long anaesthesia continued for. Rats killed at 7h. |
| **100** | Focal embolic rat model of cerebral ischaemia | yes for surgery |  | intracardiac perfusion under deep anaesthesia (overdose thiopental) | 72 hours after MCA embolism | Rats anaesthetised and surgery performed to occlude MCA by placement of clot at origin of MCA via catheter. Contrast angiography performed within 30 mins of embolisation and 3 hrs after treatment. Rats had saline or various doses/ combinations of tpa and other agents 3 hrs after embolisation. Neurologic evaluation at 2 and 24h post embolization, including resistance to lateral push. Bleeding induced by cutting off last 3 mm of tail. Rats killed at 3 days. |
| **101** | Rat model of thromboembolic stroke | yes |  | Not reported | Twenty-four hours after embolization | Rats anaesthetised and surgery performed to flush emboli into the ICA. 2, 4, or 6 hrs after embolization animals scored neurologically, tests included resistance to lateral push, being held by tail base with forelimbs on surface. Some had convulsions, some immobile. Rats with severe neurological deficit received treatment: at 2, 4, or 6 hrs either intravenous saline, tPA, or other agent, infused over 30 mins. Rats killed at 24h. Many rats died before 24h. |
| **103** | Rat model of embolic stroke, | yes |  | Not reported | Not reported | Rats anaesthetised and surgery performed to occlude MCA with a clot. After MCAO, all rats exhibited neurological deficits. Agents / saline injected 3 and 4 hrs after ischemia. MRI scans performed before and during ischemia and before and after drug treatments, for total of 6 hrs and 24 hours after embolization. Time of death not reported (presumably after 24hr scan). |
| **133** | Rabbit model of thromboembolic stroke | No information given on anaesthesia (nothing reported but clear that animals awake during embolization) | Yes | Not reported | surviving animals killed 48 hours after embolization | Rabbits catheterised (presumably under anaesthesia, not reported), given 3hrs to recover, then embolized by flushing clot into cerebral arterial system. If rabbit did not react behaviourally a second clot was injected. Most 'successfully embolized' rabbits responded with either nystagmus, pupillary dilation, hemiparesis, or brief uncoordinated jerking movements. After embolization the catheter was ligated close to the neck, and the rest cut off. 5 or 65 mins after embolization rabbits had drugs or vehicle by intravenous infusion over 30 mins. Killed 48h after embolization. |
| **134** | Rabbit Large Clot Embolic Stroke Model | No information given on anaesthesia (nothing reported but clear that animals awake during embolization) | Yes | Not reported | surviving animals killed 48 hours after embolization | Rabbits catheterised (presumably under anaesthesia, not reported), then embolized (according to Lapchak procedure, above). If rabbit did not react behaviourally, second clot injected. Agents or vehicle administered by intravenous infusion over 30 mins, starting 5 mins or 1 hr after stroke. The majority of embolized rabbits responded with behavioural manifestations including nystagmus, pupillary dilation, hemiparesis, or brief uncoordinated jerking movements. Killed 48h after stroke. |
| **104** | Rat model of mechanical focal ischemia | yes for embolisation |  | Not reported | At 30 h post embolisation | Rats anaesthetised and surgery conducted to occlude MCA for 60 mins using intraluminal filament, also to catheterise jugular vein and take blood sample. Animals allowed to recover from anaesthesia and eat and drink. Sham rats had same interventions, without occlusion. 6h after stroke TPA or saline administered by infusion pump over 1hr. In other rats, 6h after stroke, saline, tpa or tpa plus solution obtained from an earlier procedure administered. Killed 24h after stroke. |
| **105** | Rat model of focal cerebral ischamia | yes |  | transcardial perfusion under 'deep anaesthesia' | 27 hours after embolisation | Rats anaesthetised and surgery conducted to produce 3hrs of ischaemia by occluding the MCA using a monofilament. TPA infused iv at various doses over 1 hr. When thread withdrawn and reperfusion commenced animals returned to cages to awake from anaesthesia. Reperfusion period was 24 hours, after which animals killed. |
| **106** | Rabbit small clot embolism model | Yes for catheterisation but not for embolisation | Yes | Not reported | Surviving animals killed 48 hours after embolization | Rabbits anaesthetised and surgery conducted to insert catheter with distal ends left accessible outside neck. Rabbits allowed to recover for 3 hrs, then either small or large clots injected. Drugs given IV either 5 or 60 mins post embolization. Rabbits observed continuously for minimum of 2 hrs after embolization / treatment. Neurological function scored at 2 and 24 hrs post embolization. Small numbers of microclots caused no grossly apparent neurological dysfunction but large numbers invariably caused death or abnormality (ataxia, leaning, circling, lethargy, nystagmus, loss of balance, loss of sensation, paraplegia. Surviving animals killed 48 hrs post embolization. |
| **107** | Rat model of embolic stroke | Nothing recorded |  | Unclear: brains perfused – but was this how they died? | Twenty-four hours after embolization | Anaesthesia not reported. Surgery conducted to produce thromboembolic focal ischemia by introducing clots (using a catheter and syringe) into ECA. No details on catheterisation. 15 mins after clot infusion, catheter withdrawn. Tpa or saline given IV continuously for 30 mins via femoral vein at range of times post embolization, up to 2hrs. Rats killed 24hrs post embolization. |
| **108** | Rat embolic stroke model | No information on anaesthesia given |  | Not reported | 24 h after embolisation | Anaesthesia not reported, v little detail. Surgery conducted to inject blood clot into internal carotid artery. Clot formation evaluated using laser Doppler flowmetry but no information on procedures this must have entailed (skull drilling etc.). Drugs administered IV 2hrs after embolization, infusion over 1 or 4 hrs. Neurological deficits evaluated 24 hrs after embolization, after which animals killed. |
| **109** | Rat model of embolic stroke | Yes. Donor rats also anaesthetised. |  | Not reported | 24 h after embolisation | Animals anaesthetised and surgery conducted to inject microclots into ICA. Agents administered 2 and/ or 6hrs after embolisation. The skull was drilled (unclear whether during same procedure or day before?) for laser Doppler flowmetry. Animals killed 24 hrs post embolization. |
| **110** | Rat thromboembolic stroke model | Yes |  | perfused transcardially while 'deeply anaesthetised' | Unclear, seems to be 24h after surgery (but elsewhere reported 48h) | Animals anaesthetised and surgery conducted to introduce catheter into ICA, withdraw blood to form clot, introduce clot into ICA and remove catheter. Animals allowed to recover from anaesthetic. Drugs administered 2 h after embolization, either IM, IV or IP followed by a subcutaneous pump infusion 2 h after embolisation. (For this the animal was anaesthetised and the pump implanted subcutaneously on its back for continuous infusion, unclear for how long). Neuro assessments conducted 2 & 24 hrs after embolization (involving resistance to lateral push). Seizure activity observed 24 h after embolisation. 45/48 rats had seizures (rhythmic mouth / facial movement; rhythmic head nodding; spasm; rearing and spasm; rearing and falling). Confusion over when animals killed: either 24 or 48 hrs, but some died before endpoint. |
| **135** | Rat model of embolic middle cerebral artery occlusion | No information on anaesthesia given |  | Not reported | at 1 or 7 days after MCA occlusion | Anaesthesia not reported, v little other detail. Surgery conducted to occlude MCA. Agents given either IV 4 hrs post embolization, followed by a second dose IP 12 hrs after first dose, or IV at 4 hrs with continuous infusion over 30 mins. At 24 hrs post stroke rats given IV fluorescein. Neurological severity scores and foot-fault (rats walk across a grid) tests measured at 1 and 7 days post stroke. Rats in all groups exhibited severe neurological deficits and poor performance on foot-fault test 1 day post stroke. Rats killed at 1 or 7 days post stroke. |
| **136** | Rat embolic model of stroke | No information given on anaesthesia |  | Not reported | 7 days after MCA occlusion | Anaesthesia not reported. Surgery conducted to occlude MCA using a clot. At 2 or 4 hrs post stroke, animals had agents either IV initially, followed by an infusion over 30 mins, or followed by infusion over 7 days with a Harvard pump. The latter animals were allowed complete freedom of movement and access to food while maintaining the infusion (no info on pump or how placed). Neurological assessments and foot-fault tests were conducted at 1 hr and 7 days post stroke. All rats exhibited severe deficits 1 hour post stroke. Animals killed 7 days post stroke. |
| **112** | Rat model of embolic stroke | yes |  | overdose of pentobarbitol | 3h after stroke induction in one centre and 7 days after stroke induction in other centre | Rats anaesthetised and surgery conducted to induce embolic MCA stroke by injecting blood clots into ICA through an intraluminal catheter. 2 different models used. One involved catheterization and injection of a clot; other involved surgery to flush clots into ICA via ECA, plus Laser Doppler measurements (which involves drilling into skull for placement of probe). Agents with or without ultrasound given (not clear when). For ultrasound the fur on the cranial skull was shaved and ultrasound transmitted from top of skull. Experiment ended (animals killed?) either 3 hrs post stroke, 1 hr after treatment or 7 days post stroke. Some died before endpoints. |
| **113** | Rat model of focal embolic cerebral ischemia | yes |  | anesthetized and transcardially perfused | approximately 28 h after the onset of ischemia | Rats anaesthetised and surgery conducted to occlude the MCA using a clot. Rats had either no drugs or TPA at 4 hrs. Anaesthesia was maintained for MRIs which were performed before stroke, repeatedly for 6–7 h after the stroke onset and at 24 h post stroke. Movement was minimized using stereotaxic ear bars. Contrast-enhanced MRI was performed at 4, 7, and 24 h post stroke, after which animals were killed. |
| **114** | Rat model of thrombo-embolic stroke | Yes |  | Not reported | At 24 h | Rats anaesthetised and surgery conducted to occlude the MCA using a clot. Anaesthesia maintained during 8.5h of experiment. Rats had tpa either 1 or 3 hrs post stroke infused IV over 30 mins. Some rats were subjected to hypothermia at 33 degrees for 4 hrs starting 1 h post stroke, induced with ice and by spraying alcohol on the animal’s body surface. All animals had MRIs at 0.5, 3, 6, and 24 h, lasting 20 mins at each time point. For PWI, a contrast agent was injected IV. Endpoint was 24 hrs, some died earlier. |
| **115** | Rabbit model of small clot embolic stroke | Yes |  | Not reported | Not reported | Rabbits anaesthetised and surgery conducted to insert catheter into common carotid, with distal ends accessible outside the neck. Rabbits were allowed to recover from anaesthesia for a minimum of 3h after which clot particles were rapidly injected through the catheter. Drugs administered at 15, 60, 75 and 135 mins post stroke. Blood taken 5 and 60 mins after dosing. Rabbits observed for at least 2 hrs post stroke. Neurologic function scored at 24 hrs. Abnormal rabbits had ataxia, leaning, circling, lethargy, nystagmus, loss of balance, loss of sensation, paraplegia. Endpoint unreported. |
| **116** | Middle cerebral artery occlusion model | Yes for collecting blood from abdominal aortas. Yes for platelet aggregation studies yes for MCA occlusion surgery |  | cardiac perfusion under pentobarbital anesthesia | At 24 h after MCA occlusion | Animals anaesthetised and surgery conducted to insert catheter and perform craniotomy to place Doppler flow probe and to occlude MCA using Rose Bengal infusion and photo-irradiation with green light. Drugs were administered for 30 mins or 3 hrs from cessation of occlusion. After drug administration the skin incision was closed and animals allowed to recover from anaesthesia. At 24 hrs animals were examined for neurological function, taking into account circling, forelimb paralysis, hindlimb paralysis and resistance to lateral push. After neuro exam animals were killed. |
| **117** | Mouse model of MCA occlusion | Yes |  | overdose of pentobarbital then perfused with saline transcardially | 24 h after MCA occlusion | Mice anaesthetised and surgery conducted to insert catheter, cut open part of the skull above the MCA and to occlude MCA using irradiation with green light while injecting Rose Bengal. Wound closed, catheter removed. Drugs administrated 30 mins or 4 hrs post stroke. Drugs given at 30 mins were infused under anaesthesia; drugs given at 4 hrs were injected into conscious animals via a tail vein. Mice killed 24 hrs post stroke. |
| **119** | Rat model of permanent focal cerebral ischemia | Yes |  | Not reported | At 24 h or 7 days after ischemia | Rats anaesthetised and surgery conducted to insert a monofilament into MCA and to inject agents using a microsyringe after MCA occlusion. Motor deficit assessed. Animals killed at 1 or 7 days post occlusion. (Lack of detail) |
| **120** | Rat model of MCA occlusion | Yes for skull drilling. Yes for MCA occlusion surgery. |  | Not reported | Day 7 | Rats anaesthetised and surgery conducted to drill a hole in skull to measure rcbf. Animals allowed to recover. Next day rats re-anaesthetised and surgery conducted to occlude right MCA by inserting a silicon coated nylon thread into common carotid artery. After 1.5, 3, or 4.5 h of transient MCA occlusion, blood flow restored by removal of thread. Some animals were operated on but did not undergo MCAO or have drugs. Others had agents every 1.5h from just after MCAO to just before reperfusion, plus some having agents just after reperfusion as well. Endpoint day 7? |
| **137** | Rat model of MCAO | No information given on anaesthesia |  | Not reported | 7 days after MCAo (some also seem to have been killed at 24h but unclear) | Anaesthesia not reported. Rats subjected to embolic middle cerebral artery occlusion using a labelled clot. Agents given, plus follow up 12 hrs later, or by continuous infusion over 30 mins. Also, one agent administered IV at 4 hours and another IA at 6 hrs. A florescent tracer was administered IV (time point unclear). Neurological function measured 1 and 7 days after MCAO. Animals killed at 7 days post stroke, possibly some also at 24 hrs. |
| **121** | Rat model of embolic stroke | Yes |  | anesthetized  and transcardially perfused | 48 hours after MCAo | Rats anaesthetised and surgery conducted to block the MCA using a clot. Agents administered IV 4 hrs after stroke, followed by an IP dose 12 hrs later; or infused IV 4 hrs after stroke, bolus followed by 30-min infusion. MRI scans performed, anaesthesia maintained. Stereotaxic ear bars used to minimize movement during scans. Scans performed before ischemia, repeatedly for 1 hr after stroke and at 24 and 48 hrs, each taking about 2hrs. Fluorescein administered IV 5 mins before they were killed at 48 hrs. (some died at another time point but this not clear) |
| **123** | Mouse model of focal ischaemia | Yes |  | anesthetized and decapitated | 24 h after occlusion | Mice anaesthetised and surgery conducted to occlude MCA using a monofilament. 90 mins later reperfusion initiated by thread withdrawal, whereupon either tPA or saline administered by continuous infusion over 30 mins and another agent was injected intraperitoneally. Laser Doppler flow was monitored (but no mention of skull drilling to place probe). Mice killed 24 hrs post stroke. |
| **124** | Monkey model of thrombotic focal cerebral ischaemia | Yes for collecting blood from the abdominal aorta. For MCAO surgery monkeys were lightly anesthetized. Yes for endotracheal intubation. |  | surviving monkeys anesthetized and transcardiac perfusion performed | At 24 h | Monkeys were anaesthetised and surgery conducted to occlude MCA using 10 mins of photo-irradiation and 6 mins IV injection of Rose Bengal. MCA was accessed transorbitally which involved taking out the eye and performing an orbital craniotomy to allow observation of MCA and to place probe to measure blood flow. Test agents were injected from the end of photo irradiation, infused over 1 or 3 hrs. Electrolytes given. After treatment, blood flow measured continually for 3 hrs, then wound closed, the eyelids sutured together and animals given IM painkiller, allowed to recover from anaesthesia and returned to their home cage. Neurologic deficits assessed 24 hrs after MCAO. Vehicle-treated animals displayed severe neurologic deficits (unable to walk or stand) or were dead. Survivors killed at 24 hrs post MCAO. |
| **Total**  **97 studies** |  | **Anaesthesia reported: 73**  **Not reported: 11**  **Reported for some procedures or groups of animals, but not all: 13**  NB: It was generally unclear exactly how long anaesthesia was maintained for post-surgery (e.g. for MRI scans) or which were ‘non-recovery’. (A total of 19 studies were identified as being possibly non-recovery, but this is guesswork.) In 2 cases it was reported that surgery was conducted under light anaesthesia only (27; 124). Questions also arise as to why restraints (45;49;58;) and /or paralytic agents (33; 58;38) had to be used with anaesthesia if latter sufficient (distinct from where paralytics used *without* anaesthesia, as in conscious embolization ‘models’). | **11 ‘conscious during embolisation’ models** | **Not reported: 35; perfusion fixation\* 20; Pentobarbital: 13; Beuthanasia D: 2; Potassium chloride solution: 3; Thiamyl sodium: 1; ‘Terminal’: 1; KAX cocktail: 1; Sodium pentobarbital/ lidocaine/ curare: 2; thiopental: 2; decapitation: 8; frozen in liquid nitrogen: 3; C02 asphyxiation: 2; brains removed: 3; exsanguination: 2; exsanguination and thoracotomy: 2; missing: 1**  **Total 101 as some studies used more than one method)** | **Not reported: 10; missing: 1; up to 6h: 17; Between 7-24h: 7; at 24h: 35; between 24-48h: 7; at 48h: 14; at 3 days: 2; between 1-7days: 1; between 3-14 days: 2; at 7 days: 15; at 8 days: 1; at 14 days: 1; at 1 month: 1; at 2 months: 1**  **Total 115 as studies could use more than one endpoint for different groups of animals**  **NB: A**ll refer to time post embolization |  |

\*Perfusion fixation (PF): there is confusion as in some cases this appears to be done as means of death and in other cases it appears to be done after death. Where it is reported that animals are anaesthetised and then have perfusion fixation, I have assumed that PF is the manner of death; but where it says animals are given a lethal dose of anaesthesia and then have PF, I have assumed it is the former that is manner of death. NB: anaesthesia not always reported to accompany death

**Table C: Thrombolytics: Unexpected deaths and events, paralytic agents, painkillers, welfare**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study ID** | **Unexpected deaths** | **Unexpected events** | **Paralytic agent** | **Painkillers** | **Welfare** |
| **26** | 1 animal (out of 14) died due to exsanguination from femoral catheter (7%) | Not reported |  | Not reported | Constant post-operative care was maintained by the principal investigator for the duration of each experiment |
| **27** | Not reported | Not reported |  | Not reported | Not reported |
| **28** | Not reported | Not reported |  | Not reported | Not reported |
| **30** | 9 of the 14 animals died spontaneously 1 - 2 days post embolization (64%) | Not reported |  | Not reported | Not reported |
| **31** | Some rabbits died prior to completion of treatment | Not reported |  | Not reported | Not reported |
| **32** | Not reported | Not reported |  | Not reported | Not reported |
| **34** | 48 of the 140 animals died 'spontaneously' in period up to 24h post embolization (34%) | 2 animals exhibited neurological defects after anaesthesia. |  | Not reported | Not reported |
| **35** | Some animals died 'spontaneously' in the 24 hrs after embolisation. | 3 animals died prior to endpoint |  | Not reported | Not reported |
| **33** | Not reported | Not reported | Pancuronium during implantation of device | Not reported | Not reported |
| **37** | Not reported | Not reported |  | Not reported | Not reported |
| **38** | Not reported | Not reported | Tubocurarine during embolisation | Not reported | Not reported |
| **39** | Some rats died before the experiment ended | Not reported |  | Not reported | Not reported |
| **40** | Not reported | In 49 rabbits the embolus lodged in the neck vessels instead of the brain. |  | Not reported | Not reported |
| **41** | 18 out of 24 rabbits died in the 24 hour period post embolization (75%) | 1 animal died before endpoint. 1 animal had a second infarct. |  | Not reported | Not reported |
| **42** | 52 out of 90 animals died within 24 hours post embolization (58%) | Some animals were infarcted via an inadvertent procedure (e.g. air, catheter tip emboli) |  | Not reported | Not reported |
| **43** | Not reported | Not reported |  | Not reported | Not reported |
| **44** | Mortality less than 5% one week after embolisation [and 1% 8 weeks after surgery] | Not reported |  | Not reported | Not reported |
| **45** | Not reported | Not reported |  | Not reported | Not reported |
| **46** | Not reported | Not reported |  | Not reported | Not reported |
| **47** | Not reported | Not reported | Tubocurarine during embolisation | Not reported | Not reported |
| **48** | Some rats died prior to endpoint | Not reported |  | Not reported | Animals were housed in a temperature controlled house with 12 hours dark/ light cycle and free access to food and water. |
| **49** | Not reported | Not reported |  | Not reported | Not reported |
| **50** | Not reported | Not reported |  | Not reported | Not reported |
| **51** | 4 out of 68 animals had 'early deaths' (6%) | In 4 animals there were ‘technical difficulties’ or early death |  | Not reported | A reference to how depth of anaesthesia was tested |
| **52** | Not reported | One rabbit had a very large volume of ischaemia. |  | Not reported | Not reported |
| **53** | Not reported | Not reported |  | Not reported | Not reported |
| **54** | 5 out of 55 rats died (9%) | Not reported |  | Not reported | Animals were housed in a temperature controlled house with 12 hours dark/ light cycle and free access to food and water. |
| **55** | Not reported | Not reported |  | Not reported | Not reported |
| **56** | 2 out of 40 animals died due to haemorrhage (5%) | One animal had fatal systemic haemorrhage and one had fatal hypotension |  | Not reported | Not reported |
| **58** | Not reported | Not reported | Pancuronium | Not reported | Not reported |
| **126** | Not reported | Not reported |  | Not reported | Not reported |
| **125** | Not reported | Not reported | Pancuronium | Not reported | Not reported |
| **59** | 22 out of 70 rats did not survive up to 24 hours post embolisation. (31%) | Not reported |  | Not reported | Not reported |
| **62** | Not reported | Not reported |  | Not reported | Mice were housed in a 12 hours light/ dark cycle with food and water ad libitum |
| **63** | Not reported | Not reported |  | Not reported | Not reported |
| **127** | Not reported | One animal had a second infarct |  | Not reported | Not reported |
| **128** | 5 out of 24 animals died 4-24 hours post embolization due to severe cerebral oedema (21%) | Not reported |  | Not reported | Not reported |
| **64** | Not reported | Not reported |  | Not reported | Not reported |
| **66** | One animal (out of 58) died when MCA reperfused (2%) | Not reported |  | Not reported | Not reported |
| **67** | 9 out of 86 rats died within the 24h post embolisation period (10%) | Not reported |  | Not reported | Not reported |
| **68** | One animal (out of 17) died in 24 h period post embolization (6%) | Not reported |  | Not reported | Not reported |
| **69** | Not reported | Not reported |  | Not reported | Global ischaemia: animals were given access to food but not water, after the first procedure. Focal ischaemia: Animals were deprived of food but allowed free access to water the night before surgery. |
| **70** | Not reported | Not reported |  | Not reported | Not reported |
| **71** | Not reported | Not reported |  | Not reported | Not reported |
| **72** | 3 animals out of 98 (3%) died within 24 hours after embolization from massive brain oedema. | Not reported |  | Not reported | Not reported |
| **130** | 2 rats out of 72 (3%) died within 24 h from massive brain edema. | Not reported |  | Not reported | Not reported |
| **73** | Not reported | Not reported |  | Not reported | Not reported |
| **74** | One rabbit out of 69 died (1%) | In 6 animals there was mechanical/ equipment failure. 1 animal had uncorrectable hypotension and 1 died before the endpoint |  | Not reported | Not reported |
| **75** | Missing data | Missing data |  | Missing data | Missing data |
| **77** | Not reported | Not reported |  | Not reported | Not reported |
| **78** | Not reported | Not reported |  | Not reported | Not reported |
| **79** | Some animals died before endpoint | Not reported |  | Not reported | Not reported |
| **80** | Not reported | Not reported |  | Not reported | Not reported |
| **81** | Not reported | Not reported |  | Not reported | Not reported |
| **131** | Not reported | Not reported |  | Not reported | Not reported |
| **82** | Some animals died before endpoint | Some animals deemed ‘abnormal’ after catheterisation surgery. |  | Not reported | Not reported |
| **83** | Not reported | Not reported |  | Not reported | Not reported |
| **84** | Not reported | Not reported |  | Not reported | Not reported |
| **85** | Some animals died before endpoint | In 55 out of 165 animals the injected blood clot did not reach the brain. |  | Not reported | Not reported |
| **86** | Not reported | Not reported |  | Not reported | Not reported |
| **87** | Not reported | Not reported |  | Not reported | Animals were housed under diurnal lighting conditions, allowed free access to food and water before and after the experiment. |
| **89** | Not reported | Not reported |  | Not reported | Not reported |
| **91** | Not reported | Not reported |  | Not reported | Not reported |
| **92** | Not reported | Not reported |  | Not reported | Not reported |
| **93** | Not reported | Not reported |  | Not reported | Not reported |
| **94** | Reported that no intra-operative deaths or seizures occurred during the experiment | One rabbit had a minor haemorrhage at catheter site. |  | Not reported | Animals were deprived of food but allowed free access to water the night before surgery. |
| **95** | One rat out of 46 (2%) died of severe haemorrhage 7h after embolization | One animal had fatal severe haemorrhage |  | Not reported | Not reported |
| **96** | Not reported | Not reported |  | Not reported | Animals were housed at 23°C ± 2°C, 55% ± 5% humidity, under a 12-hour light/dark cycle (lights on at 7:00) for at least 1 week before use and were allowed free access to food and water. |
| **97** | Not reported | Not reported |  | Not reported | Not reported |
| **98** | 7 animals (out of 18) died before day 3 (39%) | Not reported |  | Not reported | Not reported |
| **99** | Not reported | 2 rats excluded due to 'failure in temperature or respiration control' and 5 due to uncontrolled bleeding from surgical wounds | Pancuronium bromide | Not reported | Not reported |
| **100** | Not reported | 8 animals that did not show neurologic  deficits after surgery |  | Not reported | All animals were fasted 12 hours before surgery to normalizethe blood glucose level. |
| **101** | I calculate (Table 2) that 133 rats (out of 408) died before 24 hours (33%) | Not reported |  | Not reported | Not reported |
| **103** | Not reported | Not reported |  | Not reported | Not reported |
| **133** | Some animals died before endpoint | Not reported |  | Not reported | Not reported |
| **134** | Some animals died before endpoint | Not reported |  | Not reported | Not reported |
| **104** | Less than 10% of animals died ‘for technical reasons’ during or immediately after embolization (calculate n = 9 died). Further rats died before endpoint: 8% in control group and 36% in treatment groups (n not given and difficult to calculate) | Not reported |  | Not reported | Not reported |
| **105** | Not reported | Not reported |  | Not reported | All animals had free access to food and water after their surgery. |
| **106** | Some animals died before endpoint | Not reported |  | Not reported | Throughout the study, the health status of the rabbits was closely monitored by the vet and staff on duty |
| **107** | Not reported | Not reported |  | Not reported | Not reported |
| **108** | Not reported | Not reported |  | Not reported | Not reported |
| **109** | Not reported | Not reported |  | Not reported | Not reported |
| **110** | Some animals died before endpoint | Not reported |  | Not reported | All possible efforts have been made to attenuate the suffering and death of the animals in these experiments. Food was withheld from animals for twelve hours prior to surgery to normalise blood glucose levels. |
| **135** | Not reported | Not reported |  | Not reported | Not reported |
| **136** | Not reported | Not reported |  | Not reported | Not reported |
| **112** | 7 out of 54 (13%) died early, usually due to generalized bleeding following tPA | 16 of 54 rats (29.6%) had major bleeding  complications |  | Not reported | Not reported |
| **113** | Not reported | Not reported |  | Not reported | Not reported |
| **114** | Some animals died before endpoint | Not reported |  | Not reported | Not reported |
| **115** | Not reported | Not reported |  | Not reported | Throughout the study, the vet and staff on duty closely monitored the health status of the rabbits |
| **116** | One animal died (less than 1%) | Not reported |  | Not reported | The animals were purchased at least 1 week before the experiments. They were given free access to food and water and maintained on 12-h light/dark cycle in a controlled temperature (23F1 8C) and humidity  (55F5%). |
| **117** | Not reported | Not reported |  | Not reported | Not reported |
| **119** | Not reported | Not reported |  | Not reported | All rats were allowed free access to food and water. |
| **120** | Some animals died before endpoint | Not reported |  | Not reported | Not reported |
| **137** | Not reported | Not reported |  | Not reported | Not reported |
| **121** | Not reported | Not reported |  | Not reported | Not reported |
| **123** | Not reported | Not reported |  | Not reported | Not reported |
| **124** | One animal (out of 33) died, possibly due to severe brain oedema (3%) | Not reported |  | Buprenorphine | Animals were housed at 231C7 11C, 55%75% humidity, under a 12-hour light/dark cycle (lights on at 7:00). |
| **Total = 97 studies** | **Not reported: 58**  **Reported number or percentage of deaths that occurred: 24**  **Reported that deaths occurred before endpoint but no numbers given: 13**  **Reported that no deaths occurred: 1**  **Missing data: 1**  **(Of the 24 that reported numbers of deaths, 9 did not say *when* deaths occurred; 12 reported deaths in 24 h period post embolism; 1 reported in deaths in period up to 48h; 1 up to day 3; 1 up to 8 weeks. % death rate before endpoint ranged from 1% to 75%, with a mean of 18% mortality before endpoint.)** | **Not reported: 79; studies that reported some unexpected event: 17 (of these 4 reported deaths prior to endpoint; 6 reported technical difficulties / failure of some procedures; 3 reported haemorrhage [of which 2 fatal]; major bleeding complications 2; secondary stroke 2; fatal hypotension 2; very large ischaemia 1; missing data 1; ‘abnormal’ after catheterisation 1; no neurological deficit post-surgery 1;).**  **NB: Studies could report more than one type of unexpected event.**  One author (study 85) writes about sample size calculations notes that previous experience with this stroke model indicates that there are premature losses of animals caused by various preparation difficulties or deaths after embolization before treatments can be administered | **Paralytic agents reported in 6 studies** | **Reported in 1 study** | **Not reported 79**  **Reported 18: statement about conditions animals housed in and how fed 13 (of which 4 referred to temperature, light and access to food and water, 2 referred to light cycle and food/ water, 6 referred to food/ water access only and 1 referred to temperature and light only); statement about monitoring of experiments 3; comment on how depth of anaesthesia tested 1; comment on attempts made to attenuate suffering 1; when animals purchased 1; missing data 1.**  Some of these statements were found among ethical statements. 3 studies made more than one type of statement. |

**Table D: Thrombolytics: Model**

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| **Summary of animal model**  This model involves inducing a stroke in the animal and then testing the effect of a thrombolytic agent post-stroke. On the day before surgery some animals may undergo anaesthesia and preparatory surgery, e.g. to produce a clot, or place catheters, ligatures or probes. On the day of the experiment animals are anaesthetised and undergo surgery to induce a stroke. Stroke may be surgically induced in a number of different ways, including flushing pre-fabricated blood clots into the carotid and cerebral arteries, blocking these arteries with filaments, tying the arteries or producing a thrombus with photo-illumination and photosensitive dye (Rose Bengal). During surgery they may also have their skulls opened for the placement of probes and monitors. They will be given a thrombolytic agent (or saline) intravenously. They may have angiograms, CT scans or MRI scans whilst under anaesthesia. Upon recovery animals may be observed for 2hrs to 24hrs, or observation can be extensive, over 1- 7 days, 2 weeks, or as much as 1 or 2 months, after which animals are killed. During the period of observation animals may have neurological assessments which commonly involve being held upside down by the tail, or being pushed laterally to test resistance. More detailed assessments may include assessing how long rats can remain on a horizontal suspended rotating rod, or how long it takes them to remove sticky tape from their paws. In variations of the model some animals had surgery under anaesthesia to place a catheter, then recovered, after which a stroke was induced (via a clot injected through the catheter) whilst they were awake and restrained. Some animals had surgery under anaesthesia to induce a stroke, drug treatment, then a series of MRI scans whilst restrained in a head holder and with ear bars. MRI scans could continue for up to 8h post stroke, and/or could be performed at 1, 2 or 7 days after which animals were killed. |