The Archives of Internal Medicine

Vol. XV

FEBRUARY, 1915

No. 2

ACTION OF ATOPHAN AND NOVATOPHAN IN GOUT AND IRITIS *

C. A. SMITH, M.S., AND P. B. HAWK, PH.D.
PHILADELPHIA

Since the work of Nicolaier and Dohrn¹ showing an increased elimination of uric acid, due to the action of 2-phenylquinolin-4-carboxylic acid (atophan), a great deal of work has been done by many investigators with this substance. All get results showing an increased elimination, but all are not in accord in explaining the mechanism by which this increased elimination is obtained. Weintraud,² as well as Frank and Bauch,³ have concluded from results of experiments in which uric acid was injected and sodium nucleinate was fed, that the atophan acts by increasing the efficiency of the kidney for uric acid elimination. Deutsch,⁴ Folin and Lyman⁵ and Zuelzer⁶ have reached the same conclusion by showing a decrease in the uric acid content of the blood, after the administration of atophan. Retzlaff⁷ and Brugsch,⁸ as well as Gudzent, Klemperer and Dohrn (cited by Retzlaff), were unable to obtain any decrease in the uric acid of the blood by the action of atophan, but, to the contrary, obtained an increase, which they interpret as indicating a mobilizing action of the atophan.

* Submitted for publication June 26, 1914.

* From the Laboratory of Physiological Chemistry, Jefferson Medical College.

1. Nicolaier, A., and Dohrn, M.: Ueber die Wirkung von Chinolincarbon-säure und ihre Derivate auf die Ausscheidung der Harnsäure, *Deutsch. Arch. f. inn. Med.*, 1908, xciii, 331.

2. Weintraud, W.: Zur Wirkung der Stophan bei Gicht, *Verhand. d. deutsch. Kong. f. inn. Med.*, 1911, p. 482.

3. Frank, E., and Bauch, B.: Ueber den Angriffspunkt des Atophans bei seiner Einwirkung auf die Harnsäure Ausscheidung . . . *Berl. klin. Wchnschr.*, 1911, xlviii, 1463.

4. Deutsch, F.: Ueber die Wirkung des Atophans bei Gesunden und Gicht-kranken, *München. med. Wchnschr.*, 1911, lviii, 2652.

5. Folin, O., and Lyman, H.: On the Influence of Phenylquinolin Carbonic Acid (Atophan) on the Uric Acid Elimination, *Jour. Pharm. and Exper. Ther.*, 1912-13, iv, 539.

6. Zuelzer, G.: Ueber die Diagnose der Gicht durch Atophan, *Berl. klin. Wchnschr.*, 1911, xlviii, 2101.

7. Retzlaff: Ueber Atophan Therapie bei der Gicht, *Deutsch. med. Wchnschr.*, 1912, xxxviii, 404.

8. Brugsch, T.: Diagnose, Wesen und Behandlung der Gicht, *Berl. klin. Wchnschr.*, 1912, xlix, 1597.

It appears to us, however, that although probably the primary action of the atophan is the stimulation of the kidney, for uric acid elimination, yet it is logical to think of at least an indirect mobilizing action. In normal cases and in non-gouty cases the uric acid elimination, under the influence of atophan, is rather large the first day, and falls after a day or two to a point below normal. This is apparently due to the depletion of the supply of uric acid in the blood, and as there are no deposited urates, there is no replenishment of the depleted blood. In the case of gout, however, there are deposits, which may be mobilized, tending to maintain the blood concentration, thus accounting for the rather high and long-continued increased excretion of uric acid in gout cases, as mentioned by Zuelzer.⁶ That the mobilization is not extensive is apparently indicated by the fact that the uric acid content of the blood is lower at the end of the atophan treatment. It seems reasonable to think that as the supply of uric acid in the blood is decreased through the action of atophan, there would be a tendency for the solution of the deposits.

In connection with the mobilizing of deposited urates, the work of Daniels,⁹ showing an apparent increase in the uric acid output in gout over that due to atophan, by the use of lithium along with atophan, is of interest. Abl† has suggested the use of other drugs with atophan.

Our studies were conducted on patients in the Jefferson Hospital, and in all instances the subjects were placed on purin-free diets. No attempt has been made to give complete clinical findings.

OBSERVATIONS 1 AND 2.—*Gout*.—N. W., aged 20. (Tables 1 and 2). The patient had a marked hypertrophy of the left ventricle, had had several severe dilatations, chronic interstitial nephritis, numerous tophi in the ears, and arteriosclerosis. Blood-pressure was high as a result of the arteriosclerosis.

TABLE 1.—OBSERVATION 1, GOUT

Day	Urine		Blood (100 gm.) Uric Acid mg.	Atophan gm.
	Vol. c.c.	Uric Acid gm.		
1	1,975	0.217		
2	1,625	0.068		
3	2,474	0.087		
4	2,282	0.084		
5	2,064	0.101	2.54	3
6	2,077	0.101	...	3
7	1,805	0.054	1.60 *	3
8	1,216	0.097		
9	1,898	0.127		
10	2,530	0.157		
11	2,438	0.144		
12	2,590	0.121	1.71	

* Taken at the end of Day 7.

9. Daniels, Amy L.: The Influence of Lithium and Atophan on the Uric Acid Excretion of a Gouty Patient, *THE ARCHIVES INT. MED.*, 1914, xiii, 480.

† Abl: *Arch. f. exper. Path. u. Pharmacol.*, 1914, lxxiv, 119.

TABLE 2.—OBSERVATION 2, SAME CASE AS IN TABLE 1

Day	Urine		Blood (100 gm.)	Atophan gm.
	Vol. c.c.	Uric Acid gm.	Uric Acid mg.	
1	2,182	0.205		
2	1,780	0.161		
3	1,712	0.221	4.88	5
4	1,622	0.208		5
5	1,915	0.216	3.44 *	5
6	1,370	0.147		
7	2,280	0.207		

* Taken at the end of Day 5.

There were no active symptoms of gout during the first observation, but on the morning of the final day, the patient complained of slight soreness in both great toes. The diet was supposedly continued purin-free between the two periods, but the patient received chicken at least once during that time; the exact day he received it, is, however, uncertain.

At the beginning of the second observation, both toes were swollen, inflamed and very painful. At the end of the second day of atophan treatment, the symptoms were much improved. The toes were still swollen, and at the end of the third day were about the same. After the atophan was stopped the symptoms reappeared, although not to the same extent. There was no noticeable change in the tophi, under the atophan treatment, as reported by Richter.¹⁰

In the "very severe case of gout" cited by Folin and Lyman,⁵ the atophan caused neither an increased uric acid elimination nor a diminished uric acid value of the blood, the blood containing the normal amount of uric acid. In our case, although the content of uric acid in the blood was normal, we obtained an appreciable reduction, although the increase in elimination was exceedingly slight. The case is of considerable interest because of the exceptionally low uric acid elimination.

In the case reported by Folin and Lyman, the rise in the uric acid content of the blood seems to be due to the decreased elimination. The increase noted in our case is apparently not to be accounted for in the same manner, as there was an accompanying increase in elimination.

OBSERVATION 3.—*Iritis*.—M. P., laborer, aged 55. Ulcerative keratitis. Patient was attending a brush fire and the wind blew some sparks and smoke into his eye. Previous treatment, atropin after sweats. Sweats discontinued with the start of this experiment. Discharged, much improved.

10. Richter, Paul Friedrich: Ueber Wesen und Behandlungen der Gicht, Deutsch. med. Wchnschr., 1911, xxxvii, 2361.

TABLE 3.—OBSERVATION 3, IRITIS

Day	Urine		Blood (100 gm.)	Atophan gm.
	Vol. c.c.	Uric Acid gm.	Uric Acid mg.	
3	1,000	0.263		
4	1,000	0.274		
5	1,000	0.274		
6	(Lost)			
7	1,210	0.293		
8	1,090	0.274		
9	1,000	0.270	1.4	5
10	1,000	0.307	...	5
11	1,090	0.273	0.4 *	5
12	458	0.253		
13	965	0.366		
14	1,000	0.146		

* Taken at the end of Day 11.

In the table, all urines recorded as 1,000 c.c. volume were very concentrated, and contained sedimented uric acid and urates. These were dissolved in sodium hydroxid and then the whole amount made up to 1 liter with distilled water. The volumes averaged about 300 or 400 c.c.

The iritis seemed to clear up rapidly under the influence of the atophan, although the uric acid elimination was not influenced.

OBSERVATION 4.—*Iritis*.—C. S. aged 35. Had two children, no miscarriages. No venereal infection. Never any acute articular rheumatism. Family history negative. Patient would not remain for the completion of the experiment, and would not permit of the taking of a final blood sample, for no apparent reason, except possibly because of menstruation, which occurred during the course of the experiment.

TABLE 4.—OBSERVATION 4, IRITIS

Day	Urine		Blood (100 gm.)	Atophan gm.
	Vol. c.c.	Uric Acid gm.	Uric Acid mg.	
1	1,500	0.297		
2	1,310	0.312		
3	800 *	0.206		
4	760 *	0.135		
5	1,450	0.278		
6	2,010	0.348		
7	1,295	0.317	0.66	5
8	1,005	0.225		5
9	1,065	0.169		5

* Probably some of these two samples were lost, although the nurses claimed the samples were complete.

In both cases of iritis (Observations 3 and 4), there was no appreciable increase in the uric acid elimination due to the atophan, although in the first case there appeared to be a slight delayed increase, similar to one recorded by Deutsch.⁴ Haskins¹¹ also noted a delay in the time

11. Haskins, H. D.: The Effect of Atophan and Novatophan on the Endogenous Uric Acid Excretion of Normal Men, *Jour. Pharm. and Exper. Ther.*, 1913, v, 63.

of appearance of the uric acid increase. The explanation for the lack of increase in uric acid excretion in iritis, as well as for the clearing up of the trouble under the atophan, in both our cases, is not apparent. It may be that atophan has an important action totally unrelated to uric acid. May this not be due to the antiphlogistic action of atophan which Starkenstein and Wiechowski¹² have demonstrated? We hope to investigate this point.

OBSERVATION 5.—*Acute Rheumatic Fever and Pericarditis*.—G. R., aged 18. All joints limited in motion. Distinct pain over vertebrae. Right wrist and hip most sensitive. Widal positive. Wassermann negative. Data in regard to history, both personal and family, very indefinite, although there was apparently no family history of gout. Had been receiving ferrosalicylate, and had also received, some time after the salicylate was stopped, 5 gm. of atophan per day for a period of five days. This was stopped the morning our observation period began. He had also received sodium bicarbonate, aspirin, and an occasional hypodermic injection of morphin to relieve pain. The sodium bicarbonate was continued throughout the observation period.

TABLE 5.—OBSERVATION 5, ACUTE RHEUMATIC FEVER AND PERICARDITIS

Day	Urine		Atophan gm.
	Vol. c.c.	Uric Acid gm.	
1	855	0.214	
2	710	0.212	
3	2,385 *	0.501	
4	920 †	0.313	
5	2,025	0.579	5
6	1,370	0.343	5
7	1,590	0.398	5
8	2,005	0.479	5
9	1,800	0.432	5
10	2,230	0.540	5
11	1,515	0.324	
12	2,610	0.596	
13	1,315	0.250	
14	1,825	0.593	
15	1,370	0.607	

* Patient (without our knowledge) was given two cups of water every half hour during the day, which may explain the large increase in uric acid eliminated, although little is known as to the effect of water ingestion on the uric acid output.

† Patient perspired excessively throughout the day and night.

After the atophan was stopped, previous to the observation period, the patient became worse, the pain increasing, and on Day 3 of the experimental period, patient had a temperature of 102.5. On the administration of atophan, the pain disappeared, and the patient was able to sit up in bed, feeling much improved. There was not a second relapse similar to the first during the time the patient continued under our observation.

12. Starkenstein, E., and Wiechowski, W.: Ueber die Pharmakologie des Atrophas, Prager med. Wchnschr., 1913.

According to Zuelzer,⁶ who finds in all cases of gout a rather marked increase in uric acid output, continued over a long period of time, and in all non-gouty joint affections, a smaller increase over only one or two days, this case would be considered as of a gouty nature. A similar rather high and uniform increased elimination is to be noted in the case of J. S. B., Observation 6, which case was diagnosed as gouty.

The increases of Days 12, 14 and 15 are rather peculiar, and not easily accounted for, unless as a delayed increase from the long atophan period.

OBSERVATION 6.—*Arteriosclerosis and Gout*.—J. S. B., bar-tender, aged 55. Rheumatic pains about shoulders and upper back. Alcoholic. No family history of gout or similar conditions. No previous history of rheumatism or lues.

TABLE 6.—OBSERVATION 6, ARTERIOSCLEROSIS AND GOUT

Day	Urine		Novatophan gm.
	Vol. c.c.	Uric Acid gm.	
1	1,380	0.426	
2	2,565	0.416	
3	1,970	0.384	
4	2,095	0.543	5
5	2,250	0.563	5
6	1,980	0.521	5
7	2,040	0.314	
9	2,245	0.294	
9	1,870	0.391	
10	1,790	0.403	

In this case results, similar to the usual results with atophan, were obtained with novatophan. The patient felt very much better while receiving the novatophan, and the discomfort in the shoulders returned, although not to the same extent, after the treatment was stopped. It is probable that the elimination would not have remained so uniform (see Days 4, 5 and 6) had the administration of the novatophan been continued for a longer period.

In one case in which atophan was given in tablet form, no difficulty was experienced in regard to an unpleasant taste. In the other cases gelatin capsules were used. In no case were there any untoward symptoms, as for example the scarlatiniform rash, noted by Herrick.¹³

Skorczewski and Sohn¹⁴ report that atophan urines respond in the characteristic manner to Ehrlich's diazo reaction. They are substantiated by Dohrn.¹⁵ We were unable to obtain the typical reaction in any

13. Herrick, W. W.: A Scarlatiniform Rash from Atophan, Jour. Am. Med. Assn., 1913, lxi, 1376.

14. Skorczewski, W., and Sohn, I.: Ueber einige in Atophanharne auftretende charakteristische Reaktionen, Wien. klin. Wchnschr., 1911, xxiv, 1700.

15. Dohrn, Max: Ueber Farbreaktion speziell die Diazoreaktion im Atophanharn, München. med. Wchnschr., 1912, lix, 568.

case. A similar reaction was obtained, but easily differentiated from the characteristic one.

Owing to previous difficulties experienced in the collection of blood samples, the uric acid was not determined in the blood during Observations 5 and 6. In determining the uric acid in blood, we followed slight modifications of the method of Folin and Denis¹⁶ as suggested by Myers and Fine.¹⁷ The oxalated blood was poured into about four volumes of boiling distilled water, with stirring, and again brought to a boil. Hundredth-normal acetic acid was then added to complete coagulation, about an equal amount being required. The procedure from this point on was the same as the original. In all cases (both blood and urine) three drops of concentrated hydrochloric acid, instead of one drop as called for by the method of Folin and Denis¹⁸ were added along with the hydrogen sulphid used to decompose the silver urate.

We wish to express our indebtedness to Drs. McCrae, Solis-Cohen, Hansell and Sweet of Jefferson Hospital for permission to study the cases herewith reported. We are also indebted to Drs. Burns, Clerf, Dry, Livengood, Lummis, Shannon, and Wayland, as well as the nurse in attendance, for care and assistance in the collection of blood samples and the handling of the cases.

16. Folin, O., and Denis, W.: A New (Colorimetric) Method for the Determination of Uric Acid in Blood, *Jour. Biol. Chem.*, 1913, xiii, 469.

17. Personal communication.

18. Folin, O., and Denis, W.: *Jour. Biol. Chem.*, 1913, xiv, 95.