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BRIEF REPORT

Self-limited febrile syndromes temporally associated with the use of propofol for sedation in gastrointestinal endoscopic procedures†

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SUMMARY

Purpose To investigate cases of febrile illnesses in patients who received propofol for sedation during gastrointestinal endoscopy.
Methods Active case finding for patients who underwent endoscopy between 1 April and 30 May 2007 and suffered unexplained fever, chills, or myalgia within 48 hour after the procedure. We reviewed medications and clinical practices to find factors associated with the reactions.
Results Seventy-four cases at eight facilities in five states were identified yielding a rate of 36 reactions per 1000 procedures, compared with a baseline rate of 0.6 per 1000. The majority of patients experienced self-limited fever (89.2%), chills (73.0%), or myalgia (63.5%). Blood samples from five patients were collected for culture; no organisms grew. All health care facilities that reported cases and fully participated in the investigation ($n = 7$) had received a common lot of propofol just before recognition of the first case. Bacterial endotoxin and sterility testing on unopened vials from this lot of propofol showed no abnormalities. Cases terminated after facilities stopped using the associated lot of propofol.
Conclusions We found a temporal association between a particular lot of propofol and an outbreak of febrile illnesses at several healthcare facilities performing endoscopy. When propofol is used to sedate patients for endoscopy, fever is a rare outcome and healthcare professionals should investigate clusters of these reactions. Post-procedure surveillance is important to identify possible medication reactions. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — propofol; fever; adverse effects; endoscopy; disease outbreak

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INTRODUCTION

An estimated 15 million endoscopy procedures are performed annually in the United States.[1] Propofol, a lipid-based anesthetic has become the sedative of choice for endoscopy because it provides rapid induction (i.e., 30–60 second); maintains a steady level of sedation, which is associated with patient comfort; and has a 30–90 minute half-life, which allows for rapid recovery.[2] Adverse effects may include apnea, arrhythmia, hypotension, or skin rash.[3] According to the package insert, fever, chills, or myalgia occur in less than 1 per cent of cases.[3] Beginning in May 2007, we investigated outbreaks of febrile syndromes following endoscopic procedures where propofol was used as the anesthetic.

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METHODS

Identification of cases

Inquiries for cases of febrile illness after endoscopy were circulated by electronic networks and faxes to providers. Providers who reported cases were asked to provide demographic and clinical characteristics and details of the endoscopic procedures. A possible case was defined as a patient who underwent endoscopy between 1 April and 30 May 2007 with (1) onset of one or more of the following: subjective fever, chills, or myalgias within 48 hour following the procedure and (2) no other suspected etiology. A probable case had at least two symptoms and a measured temperature equal to or higher than 100.3°F (38.0°C).

Evaluation of healthcare facilities

Facilities reporting two or more cases of febrile illnesses were asked to complete a questionnaire covering demographics, medications and supplies, and practices of clinicians.

Febrile illness rates were calculated for each facility that completed the questionnaire. Rates were calculated for either a 2-week period starting with the day of the first case or for the period between the first and last case, whichever was longer. We selected 2 weeks because there was general consensus among the facilities that it took 2 weeks to use all of the propofol vials in a particular lot. For comparison, we also determined post-endoscopy febrile illness rates at several other endoscopy centers that use propofol for anesthesia and perform routine telephone follow-up of patients but did not report cases during the outbreak.

Laboratory evaluation of propofol

CDC laboratories performed bacterial endotoxin (Pyros Kinetix, Associates of Cape Cod, Inc., Woodshole, MA) and sterility testing on unopened vials from the common lot of propofol. No propofol from open vials was available for testing.

RESULTS

Cases of febrile illness

During April and May 2007, 74 patients at eight healthcare facilities in five states reported febrile syndromes after endoscopy (Figure 1). Thirty-six (49%) cases were classified as probable, while 38 (51%) were classified as possible (Table 1). The number of cases for each facility ranged from 3 to 21. The overall rate of febrile illnesses was 36 per 1000 procedures (range for each facility: 6.0–103.0). By comparison, data from other endoscopy centers on febrile reactions following endoscopy when propofol is used for sedation revealed a rate of 0.56 reactions per 1000 procedures (95%CI: 0.26, 0.88).

Cases occurred in patients undergoing colonoscopy (46, 62.2%), esophagogastroduodenoscopy (19, 25.7%), or both (9, 12.2%). The majority of case–patients had fever (89.2%) and chills (73.0%) starting within 24 hour of their procedures, with a mean measured temperature of 101.2°F (38.4°C). Some

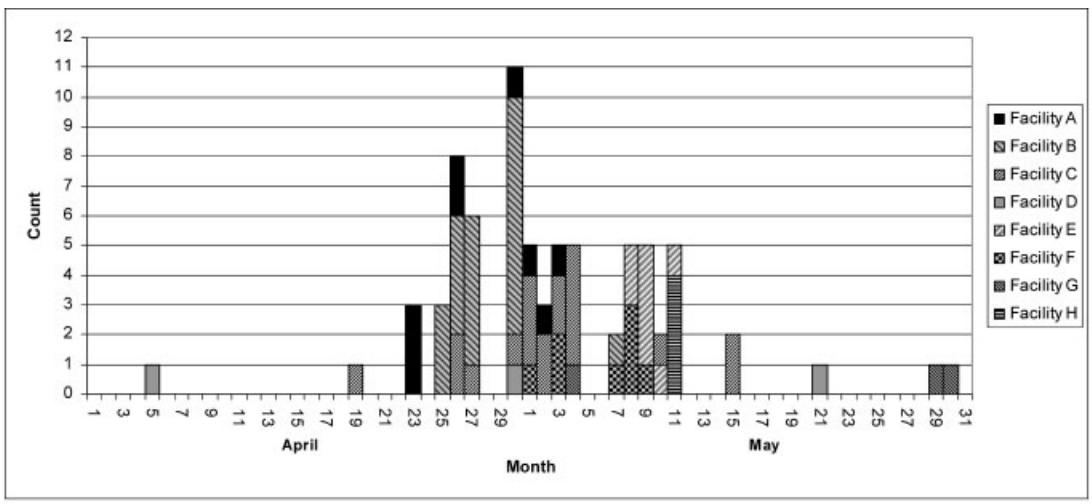

Figure 1. Febrile syndromes after endoscopy in 74 patients at eight healthcare facilities in five states, April–May 2007. Facilities include A and B in PA, C and D in NJ, E and F in NY, G in MA, and H in TN

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Table 1. Clinical features of 74 patients with febrile syndromes after endoscopy at eight health care facilities in five states*

Characteristic	Value†
Facility	
A	9 (12.2)
B	21 (28.4)
C	19 (25.7)
D	3 (4.1)
E	8 (10.8)
F	7 (9.5)
G	3 (4.1)
H	4 (5.4)
Procedure	
Upper endoscopy	19 (25.7)
Colonoscopy	46 (62.2)
Both	9 (12.2)
Case definitions	
Probable	36 (48.7)
Possible	38 (51.3)
Symptoms	
Fever	66 (89.2)
Highest temperature (°F), (49)‡	101.2 (1.2)
Chills	54 (73.0)
Myalgia	47 (63.5)
Headache	19 (25.3)
Anorexia	18 (24.0)
Sweat	18 (24.0)
Nausea	15 (20.0)
Vomiting	3 (4.0)
Fatigue	27 (36.0)
Others	27 (36.0)
Follow-up care	39 (52.7)
Called doctor	30 (40.5)
Outpatient clinic visit	10 (13.3)
Emergency department visit	15 (20.0)
Received antibiotics	8 (10.7)
Hospitalized	1 (1.3)
Labs in follow-up	
Creatinine (mg/dL), (6)‡	1.0 (0.2)
ALT§ (IU/L), (4)‡	26.5 (11.7)
Leukocytes ($\times 10^3$ cells/mcL), (8)‡	6.1 (2.2)
Percentage neutrophils (%), (7)‡	78.7 (14.0)
Absolute eosinophil count (cells/mcL), (6)‡	200 (400)
Hematocrit (%), (7)‡	41.8 (5.3)
Blood cultures	
No growth	5 (6.8)
Growth	0

*Facilities include A and B in PA, C and D in NJ, E and F in NY, G in MA, and H in TN.
†Reported as count data (%) or mean (standard deviation).
‡Number of patients with values to contribute to the calculation of the mean.
§ALT, alanine aminotransferase.

patients also reported myalgia (63.5%), fatigue (36.0%), and headache (25.3%). Symptoms were self-limited, resolving within 48–72 hour. Ten patients sought care at outpatient clinics, and 15 visited emergency departments. One patient was hospitalized overnight. In the eight patients who had their blood collected, there were no hematologic or serum chemistry abnormalities, and blood cultures from five patients showed no growth.

Healthcare facility characteristics

Eight healthcare facilities, all of which were outpatient endoscopy clinics, reported clusters of febrile syndromes. The only product common to all seven of the eight facilities that provided detailed information was propofol. Each of these clinics had received the same lot of propofol from a common manufacturer immediately before the occurrence of the first case. Five of seven facilities reported that propofol was used for multiple patients but was always used within 6 hour of opening the vial. Six of the seven facilities also used the same brand of lidocaine. However, a variety of different size vials were used, and the manufacturer verified that each size vial of lidocaine is produced separately and given a different lot number.

Product investigation

Sixty-seven cases (90.5%) occurred between 23 April and 11 May 2007 (Figure 1). The common lot of propofol used at the facilities was produced in early April and then distributed throughout the United States between 19 and 26 April 2007. Before distribution, the lot had passed all quality control tests. Sterility and bacterial endotoxin tests completed by CDC showed no evidence of microbial contamination and no detectable endotoxin.

DISCUSSION

Seventy-four patients at eight health care facilities in five states developed febrile illnesses after endoscopy in April and May 2007. A temporal association was found between onset of cases and receipt of a particular lot of propofol at that facility. Soon after the outbreak was recognized, the manufacturer sent a letter to recipients of propofol advtising them of the investigation. The US Food and Drug Administration (FDA) also released a health advisory on 15 June 2007, describing the temporal relation between the particular lot of propofol and febrile illnesses.[4]

The cause of the febrile reactions is unknown. Although intrinsic microbial or endotoxin contamination of the lot was not found, other forms of contamination with some type of antigen could explain the simultaneous occurrence of these cases at different health care facilities. The presence of these antigens might have resulted in the self-limited febrile reactions described in this report. This explanation would seem to fit best with the clinical syndromes observed in these cases because the onset of symptoms occurred later than would be expected for endotoxin contamination,

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and there was no evidence of infections in the patients who were evaluated. Why these reactions were seen only after endoscopic procedures and not after other outpatient procedures in which propofol was used as a sedative (e.g., outpatient surgery) remains unclear. One possible explanation is that transient, post-procedure reactions are more common in surgical patients and hence less likely to be reported.[5]

Beyond the potential association with a common lot of propofol, our investigation lead to two interesting findings. First, propofol is often not handled according to its labeling. Propofol's lipid base makes it highly susceptible to microbial contamination and several outbreaks related to extrinsic contamination of propofol have been reported.[6–10] Consequently, propofol has specific handling instructions to help prevent extrinsic contamination. Vials are labeled for single patient use only and unused product should be discarded within 6 hour.[11,12] Because of the expense of the medication, however, propofol is often used for multiple patients, a practice that was reported by most of the facilities that participated in this investigation. Second, data on febrile reactions following endoscopy from centers that did not experience outbreaks revealed that these are quite rare when propofol is used, less than 1 per 1000 cases in our investigation. A fever, therefore, should be recognized as a rare complication of propofol exposure.

This investigation had several limitations. We were unable to identify a cause of the reactions. Our inability to perform detailed chemical analyses on the product limited our ability to rule out a chemical or antigen contaminant as a possible cause. We are also not certain whether the lack of reports from other centers represents under-reporting, lower recognition, an intermittent problem with the lot, or some combination of these factors. It is also possible that some facilities simply elected not to use the suspect lot upon receiving the notice of the investigation from the manufacturer and FDA. Finally, lot numbers of medications could not be tracked after distribution from the manufacturer. Subdistributors did not record the lot numbers of propofol that they had distributed to end-users, and health care facilities did not record the lot numbers given to patients, nor the beginning and end dates of use of particular lots at the facility. Hence, we were not able to ascertain with certainty which lot of medications patients were exposed to.

Our investigation underscores the challenges of conducting investigations of possible adverse drug events. Fortunately, solutions are available for many of these challenges. Medication tracking would be improved if facilities recorded the dates they begin using specific lots of products. In future, the availability of barcoding technology may facilitate the tracking of medication lots to individual patients. Adverse drug event reporting can be improved if clinicians maintain a low threshold for reporting possible adverse drug reactions to public health officials for further investigation. Similar to the information that we gathered in our investigation, more data on the true rates of adverse reactions can facilitate the recognition of abnormal reactions. Furthermore, post-procedure follow-up, as done by each facility participating in this investigation, could greatly improve the detection of reactions that occur after patients go home. Investigations of medical products as possible causes of adverse reactions are important and require ongoing partnerships among industry, academia, and public health.

KEY POINTS

- We identified a large increase in self-limited febrile illnesses after gastrointestinal endoscopy at eight healthcare facilities in a 2-month period in 2007.
- There was a temporal association between receipt of a particular lot of propofol at a facility and onset of the first cases.
- There are several challenges to investigating possible adverse drug reactions in outpatient endoscopy clinics, including challenges in tracking medication lots and identifying reactions that may occur after patients have gone home.
- Recording the dates when specific lots of medications are used within a facility can enhance medication safety by facilitating investigations of potential adverse drug events.
- Post-procedure follow up with patients can be very useful in identifying potential adverse drug reactions.

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