Pattern of Dipyrone Exposure in Texas, 1998 to 2004

Mathias B. Forrester, BS^a

^a Texas Department of State Health Services, Austin, TX

ABSTRACT

Introduction: Dipyrone is an analgesic and antipyretic agent. The purpose of this study was to describe the pattern of dipyrone exposures reported to poison centers.

Methods: Human dipyrone exposures reported to 6 Texas poison centers from 1998 to 2004 were identified. Isolated and non-isolated cases were compared with respect to various factors.

Results: When compared to the Census, dipyrone exposures were significantly more likely to have been reported from regions closer to the Mexican border (53% vs 9%). Of 81 dipyrone exposures, 52 (64%) were isolated and 29 (36%) were non-isolated. Most of the dipyrone exposures occurred at the patient's own residence (72/76 or 95%) and the patients were more likely to be female (54/81 or 67%). Although the majority of both types of dipyrone exposures were adults (47/78 or 60%), children, less than 6 years of age, accounted for a higher proportion of isolated exposures (33% vs 10%) while a higher proportion of non-isolated exposures involved older children (28% vs 8%). Twenty-two percent (11/51) of isolated cases were intentional while 59% (17/29) of non-isolated cases were intentional. Of those cases with a known medical outcome, the medical outcome was no adverse clinical effect for 76% (16/21) of isolated exposures and 42% (8/19) of non-isolated exposures. The specific adverse clinical effects reported for isolated exposures were primarily neurological (n = 6), gastrointestinal (n = 4), and dermal (n = 3). The most frequently reported treatment for isolated exposures was some form of decontamination (n = 11).

Conclusions: Isolated and non-isolated dipyrone exposures varied with respect to patient age, exposure reason, management site, medical outcome.

INTRODUCTION

Dipyrone (metamizole) is a water soluble pyrazolone nonsteroidal anti-inflammatory agent used as an analgesic and antipyretic. Dipyrone's method of action is inhibition of cyclooxygenase, arachidonic acid-induced platelet aggregation, synthesis of platelet thromboxane, and synthesis of prostaglandins E_1 and E_2 [1–3].

Agranulocytosis, a serious and potentially deadly condition involving an insufficient number of the white blood cells neutrophils or granulocytes, has been associated with dipyrone use;

although, the rate of agranulocytosis among dipyrone users has demonstrated wide variation between populations. As a result of the association of agranulocytosis with dipyrone, the drug has been banned in the United States, Canada, Japan, and certain countries in Europe. However, dipyrone is still available in Latin American countries (including Mexico), some European countries, Israel, Africa, and Asia [4–6].

In Mexico, dipyrone is available under a variety of names such as Neomelubrina, Magnopiol, Conmel, and Buscapina composition. It can be obtained over the counter in the form of tablets,

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Corresponding Author: Mathias B. Forrester, BS, Epidemiology and Disease Surveillance Unit, Texas Department of State Health Services, 1100 W 49th Street, Austin, TX 78756. Email: mathias.forrester@dshs.state.tx.us

capsules, suspensions, syrup, injections, and suppositories, and dipyrone is available alone or in combination with other drugs in cold/flu preparations, antispasmodics, and vitamins [5–7].

Although dipyrone has been banned in the United States since 1979, the drug may still be bought in Mexico and brought across the border. Moreover, dipyrone-containing products have been found for sale in Latin markets in the United States [8]. As a result, people in the United States may be exposed to a drug with potentially adverse effects with which health care providers in this country may be unfamiliar [7].

There is not much published information from poison centers about the adverse exposures to dipyrone. In Israel, where the drug is legal, one study examined 243 dipyrone exposures [4]. Review of the literature failed to identify any information on dipyrone exposures involving poison centers in the United States, where the drug has been banned for 25 years. The objective of this investigation was to examine the pattern of dipyrone exposures reported to Texas poison centers during a recent seven-year period.

METHODS

This was a retrospective study using data from the Texas Poison Center Network (TPCN). The TPCN consists of 6 poison centers that collectively service the entire state. All the poison centers use the same Toxicall software and Toxic Exposure Surveillance System (TESS) database to record information on all calls received. The poison centers collect data in a similar manner.

Cases consisted of all human dipyrone exposures reported to the TPCN from 1998 to 2004. The distribution of calls was determined by year, caller location, and number of additional substances involved in the exposure. Caller location was examined in 2 ways: (1) whether the location was in one of the 2 poison centers that border Mexico versus the 4 poison centers that do not and (2) whether the location was within one of the 14 counties that border Mexico versus the 240 counties that do not.

The cases were then grouped into two categories of exposure: (1) isolated (only dipyrone was involved in the exposure) and (2) non-isolated (dipyrone and at least one other substance were involved in the exposure). These categories were chosen because a portion of all dipyrone exposures reported to poison centers might be expected to involve other substances. Thus, poison centers might find information on non-isolated exposures useful. Moreover, it might be expected that the patient characteristics, management of the exposure, and medical outcome might vary depending on the presence or absence of other substances in the exposure. The type and number of other drugs and ethanol involved in dipyrone exposures was described.

The distribution of isolated and non-isolated dipyrone exposures was calculated for patient age and gender, reason and site of exposure, management site, and medical outcome. The groupings for these variables were based on those used in the TESS database. Medical outcome was defined according to the following criteria: *no effect* (no symptoms due to exposure), *minor* (some minimally troublesome symptoms), *moderate* (more pronounced,

prolonged symptoms), *major* (symptoms that are life-threatening or cause significant disability or disfigurement), and *death*. All of the variables may not have been known for all of the exposures, so the sum for each factor may not equal the total number of human exposures. Patient ethnicity could not be examined because such information is not systematically collected by the TPCN. In 2001, the TPCN began noting which calls were handled in Spanish; however, there is some question whether this information was consistently collected.

The distribution of adverse clinical effects and treatments identified among isolated dipyrone exposures, regardless of the medical outcome (including unknown), was determined. Since adverse clinical effects and treatments were not known for human exposures from 1998 to 1999, these 2 years were excluded from the analysis of clinical effects and treatments.

Differences between types of exposures were analyzed for statistical significance by calculating the rate ratio and 95% confidence intervals using Poisson probability.

RESULTS

The TPCN received 229 total calls involving dipyrone from 1998 to 2004. Of these calls, 81 (35.4%) were human exposures, 69 (30.1%) drug identifications, and 79 (34.5%) requests for other information.

The dipyrone exposures demonstrated no clear annual trend during the seven-year period, ranging from 6 to 16 reported exposures per year.

Table 1 presents the distribution of human exposures by caller location. The caller was significantly more likely to be in a poison center bordering Mexico and in a county bordering Mexico.

Of the 81 dipyrone exposures, 52 (64.2%) were isolated and 29 (35.8%) were non-isolated, involving from 1 to 6 additional substances. *Table 2* shows other drugs and ethanol use reported with dipyrone exposures. Other analgesics were reported in 45% of non-isolated cases. The most frequently reported other drug was, the analgesic, acetaminophen.

Table 3 compares isolated and non-isolated dipyrone exposures with respect to various factors. For both types of exposures, the patients were more likely to be females. Although the majority of isolated and non-isolated dipyrone exposures were adults, a higher proportion of isolated exposures involved children less than 6 years of age while a higher proportion of non-isolated exposures involved older children.

Non-isolated exposures were significantly more likely to be intentional, particularly suspected suicide attempts. Almost all of the dipyrone exposures occurred at the patient's own residence. In the majority of isolated and non-isolated exposures, the patient was already at or en route to a health care facility when the poison center was contacted. However, a higher percentage of isolated dipyrone exposures were managed outside of a health care facility while a higher percentage of non-isolated exposures were referred to a health care facility by the staff of poison centers.

TABLE 1. Dipyrrone exposures reported to the Texas Poison Center Network from 1998 to 2004 by caller location

Caller location	Total population ¹		Human exposures		
	No.	%	No.	%	RR ²
Poison centers					
Bordering Mexico	5,113,317	24.5	55	69.6	2.84 ³
Not bordering Mexico	15,738,503	75.5	24	30.4	0.40 ³
Total known	20,851,820		79		
Counties					
Bordering Mexico	1,961,542	9.4	42	53.2	5.65 ³
Not bordering Mexico	18,890,278	90.6	37	46.8	0.52 ³
Total known	20,851,820		79		

¹ According to 2000 Census

² Ratio of human exposure % to total population %

³ Statistically significant, i.e., 95% confidence interval does not include 1.00

TABLE 2. Distribution of human exposures involving dipyrrone reported to the Texas Poison Center Network from 1998 to 2004 by the other drugs and ethanol involved in the exposure

Substance category	Number	% of total cases (n = 81)	% of non-isolated cases (n = 29)
Analgesics	13	16.0	44.8
Acetaminophen	5	6.2	17.2
Ibuprofen	2	2.5	6.9
Other analgesics	6	7.4	20.7
Anesthetics (lidocaine)	1	1.2	3.4
Anticholinergic drugs (butylhyoscine, hyoscine)	2	2.5	6.9
Anticoagulants (warfarin)	1	1.2	3.4
Antihistamines (cinnarizine, ranitidine)	2	2.5	6.9
Antimicrobials (penicillin, sulfamethoxazole and trimethoprim, tetracycline)	3	3.7	10.3
Cold and cough preparations	1	1.2	3.4
Gastrointestinal preparations (lidamidine, scopolamine, trimebutine)	3	3.7	10.3
Hormones and hormone antagonists (cyclofenil)	1	1.2	3.4
Narcotic antagonists (naloxone)	1	1.2	3.4
Vitamins (folic acid, vitamin B12)	2	2.5	6.9
Ethanol	2	2.5	6.9
Miscellaneous drugs (misoprostol)	1	1.2	3.4
Unknown drugs	4	4.9	13.8

A given human exposure might involve multiple substances in more than one category

Non-isolated cases = exposures involving dipyrrone and one or more other substances

TABLE 3. Distribution of human exposures involving dipyrrone reported to the Texas Poison Center Network from 1998 to 2004 by various factors

	All exposures		Isolated exposures ¹		Non-isolated exposures ¹		
Factor	No.	%	No.	%	No.	%	RR ²
Patient gender							
Male	27	33.3	16	30.8	11	37.9	0.81
Female	54	66.7	36	69.2	18	62.1	1.12
Total known	81		52		29		
Patient age (years)							
<6	19	24.4	16	32.7	3	10.3	3.16
6–19	12	15.4	4	8.2	8	27.6	0.30
≥20	47	60.3	29	59.2	18	62.1	0.95
Total known	78		49		29		
Exposure reason							
Unintentional	34	42.5	27	52.9	7	24.1	2.19
General	23	28.8	20	39.2	3	10.3	3.79 ³
Therapeutic error	7	8.8	5	9.8	2	6.9	1.42
Misuse	4	5.0	2	3.9	2	6.9	0.57
Intentional	28	35.0	11	21.6	17	58.6	0.37 ³
Suspected suicide attempts	21	26.3	7	13.7	14	48.3	0.28 ³
Misuse	3	3.8	3	5.9	0	0.0	-
Abuse	1	1.3	0	0.0	1	3.4	0.00
Unknown	3	3.8	1	2.0	2	6.9	0.28
Adverse drug reaction	18	22.5	13	25.5	5	17.2	1.48
Total known	80		51		29		
Exposure site							
Own residence	72	94.7	47	94.0	25	96.2	0.98
Other residence	2	2.6	2	4.0	0	0.0	-
School	2	2.6	1	2.0	1	3.8	0.52
Total known	76		50		26		
Management site							
On site (not health care facility)	21	26.3	17	33.3	4	13.8	2.42
At/en route to health care facility	52	65.0	31	60.8	21	72.4	0.84
Referred to health care facility	6	7.5	2	3.9	4	13.8	0.28
Other	1	1.3	1	2.0	0	0.0	-
Total known	80		51		29		

TABLE 3. (continued)

Factor	All exposures		Isolated exposures ¹		Non-isolated exposures ¹		
	No.	%	No.	%	No.	%	RR ²
Medical outcome							
No effect	24	60.0	16	76.2	8	42.1	1.81
Minor effect	14	35.0	4	19.0	10	52.6	0.36
Moderate effect	1	2.5	0	0.0	1	5.3	0.00
Major effect	1	2.5	1	4.8	0	0.0	-
Death	0	0.0	0	0.0	0	0.0	-
Total known	40		21		19		

¹Isolated exposures = exposures involving only dipyrone. Non-isolated exposures = exposures involving dipyrone and one or more other substances

²Ratio of isolated exposure % to non-isolated exposure %

³Statistically significant, i.e., 95% confidence interval does not include 1.00

The medical outcome was known for 49.4% (40/81) of all dipyrone exposures (21/52 or 40.4% of isolated exposures and 19/29 or 65.5% of non-isolated exposures). Isolated exposures were twice as likely as non-isolated exposures to have a medical outcome classified as no effect. A higher proportion of non-isolated exposures involved at least minor effects. No deaths were reported with dipyrone exposures.

Table 4 contains the distribution of adverse clinical effects and treatments among the 39 isolated exposures reported from 2000 to 2004. Specific adverse clinical effects were recorded for 12 (30.8%) of the cases. The highest proportion of cases had neurological effects, followed by gastrointestinal and dermal effects. The most frequently reported specific adverse clinical effect was vomiting. No specific treatment was listed for the majority of cases. The most frequently reported type of treatment was decontamination, most frequently by administration of charcoal. Treatment other than decontamination was reported in only 5 of the cases.

DISCUSSION

This study described the pattern of dipyrone exposures reported to Texas poison centers during a recent 7 year period. Although dipyrone has been banned in the United States since 1979, it is available in Mexico and can be brought over the border into the country or even purchased in ethnic markets [4–8]. As a result, people in the United States may be exposed to a drug with potentially adverse effects with which health care providers in the country may be unfamiliar [7]. Thus, information on exposures occurring in the United States might be useful to health care providers.

There were various limitations to this study. The primary limitation is the use of poison center data: reporting adverse exposures to dipyrone to the poison centers is voluntary. Thus data

on dipyrone exposures is not likely to be complete and may contain biases. Moreover, the small number of cases limited the ability to identify statistically significant differences. Not examining dosage was another limitation.

Furthermore, no attempt was made to compare the cases within the isolated and non-isolated dipyrone categories by final medical outcome. This was not done because there were only a total of two cases classified as involving moderate or major effects. Cases with minor effects could be grouped with these two cases and the whole group compared to those cases classified as no effect. However, this would assume that those cases with minor effects would substantially differ from those cases with no effect. Moreover, if the analysis of final medical outcome were limited only to isolated or non-isolated dipyrone exposures, then the number of cases in the analyses would be much smaller.

Only 35% of all calls relating to dipyrone received by Texas poison centers involved actual exposures; the rest were information calls. This might be understandable, considering that dipyrone is banned in the United States and thus may be unfamiliar to those encountering it in this country.

Dipyrone exposures in Texas were substantially more likely to be reported in those areas closer to Mexico. This might be expected because people living closer to Mexico might have greater opportunity to obtain drugs from Mexico. Moreover, the 2000 Census reported that the rates of Hispanics in Texas to be generally higher in areas closer to the Mexican border. Hispanics, particularly those who originated south of the border, might be more inclined to seek out drugs with which they are familiar. Thus regions in the United States that border Mexico might have higher rates of dipyrone use. However, one study reported dipyrone use in Utah [8]. Health care providers in regions hundreds of miles from the Mexican border might have to handle adverse exposures to dipyrone.

TABLE 4. Adverse clinical effects and treatments among isolated human exposures involving dipyrone (n = 39) reported to the Texas Poison Center Network from 2000 to 2004

	Number	% of cases
Adverse clinical effects		
Neurological	6	15.4
Agitation	1	2.6
Ataxia	1	2.6
Dizziness	1	2.6
Drowsiness	2	5.1
Seizures	1	2.6
Dermal	3	7.7
Erythema	1	2.6
Hives	1	2.6
Pruritus	1	2.6
Gastrointestinal	4	10.3
Nausea	1	2.6
Vomiting	3	7.7
Other	1	2.6
Treatments		
Decontamination	11	28.2
Cathartic	4	10.3
Charcoal	8	20.5
Food	3	7.7
Lavage	2	5.1
Other	5	12.8
Anticonvulsant	1	2.6
Antiemetic	1	2.6
Antihistamine	1	2.6
Fluids IV	2	5.1
Other	2	5.1

*A given exposure might involve multiple adverse clinical effects or treatments
Isolated cases = exposures involving only dipyrone.*

Thirty-six percent of all reported dipyrone exposures involved other substances. The most frequently reported drugs used in association with dipyrone were analgesics, particularly acetaminophen.

Isolated and non-isolated dipyrone exposures were similar in that the majority of exposures involved female patients and the exposures occurred at the patient's own residence. However, the

two types of exposures differed in other aspects. Most of the isolated exposures involved adults, followed by children less than 6 years of age. Although the majority of non-isolated exposures were also among adults, older children were among the next highest proportion. Isolated exposures were most frequently unintentional whereas non-isolated exposures were much more likely to be intentional, particularly suspected suicide attempts. In most instances, of both types of dipyrone exposures, when the patient was already at or en route to a health care facility when the poison center was contacted, a higher proportion of isolated exposures were managed outside of health care facilities. Seventy-six percent of the isolated exposures with known medical outcomes were classified as no effect, with most of the remainder classified as "minor effect." In contrast, over 50% of non-isolated exposures were classified as "minor effect."

Specific adverse clinical effects were recorded for only 31% of isolated dipyrone exposures, and only 1 to 3 cases were reported with a specific adverse clinical effect. These adverse clinical effects were most frequently neurological, followed by gastrointestinal and dermal. In several studies, observed adverse reactions to dipyrone are primarily dermal [9,10]. Reported treatment was primarily decontamination, most frequently by charcoal.

A previous investigation examined 243 isolated dipyrone exposures reported to a poison center in Israel, where dipyrone is not banned [4]. The current and previous studies are similar in that both found the majority of exposures to involve female patients, to be unintentional, to have occurred at the patient's own residence, to have a medical outcome classified as no effect, and to involve similar adverse clinical effects. Treatment of isolated dipyrone exposures was also similar in the two studies. Any differences between the results of the two studies could be due to chance, differences in the management or recording of cases, differences in the population studied, or the fact that dipyrone was legal in Israel but banned in Texas.

In summary, dipyrone exposures in Texas reported to poison centers were more likely to occur in areas closer to the Mexican border. The majority of exposures involved no other substances. Isolated and non-isolated dipyrone exposures differed with respect to patient age, exposure reason, management site, and medical outcome. Reported isolated dipyrone exposures did not tend to involve serious adverse effects and were treated by decontamination. This information may provide guidance to health care providers who are unfamiliar with this drug. Although banned in the United States, dipyrone is used in the country.

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