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The Acetaminophen Experience in South Florida

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ABSTRACT: Toxicology records of the Dade County Medical Examiner Department were reviewed for the years 1972 to 1981. Any case in which acetaminophen was detected, regardless of the cause of death, was included in the study. Of 95 cases where acetaminophen was detected, no trends were observable in age, sex, or race. Acetaminophen deaths have increased in recent years, probably because of increased marketing of products containing this substance. Some two thirds of the cases involved suicides or accidental deaths, with 40 cases being directly attributable to overdose with a variety of drugs. It is suggested that acetaminophen may be a useful indicator of polydrug overdoses.

KEYWORDS: toxicology, acetaminophen, screening procedures

Acetaminophen (*N*-acetyl-*p*-aminophenol) has analgesic and antipyretic properties (Fig. 1). It was introduced into medical use in 1893 [1] but did not gain popularity until the 1950s, when it was aggressively advertised in the United States. The most well-known brand name, Tylenol®, was introduced in 1955; Darvocet-N® followed in 1972. The latter is a combination of acetaminophen and propoxyphene. From 1970 to 1981, the *Physician's Desk Reference* listing of acetaminophen preparations increased from about 45 to 85. Television advertisements for acetaminophen compounds are commonplace. The adult consumer has a choice of an "extra strength" acetaminophen product, 500 mg, and the 325 mg of acetaminophen "regular strength" preparations.

This study deals with the use and abuse of acetaminophen in Dade County, Florida, over a ten-year period, 1972 through 1981. The purpose of this study is to determine any trend in the use and abuse of acetaminophen during this period.

Methods and Materials

The toxicology records of the Dade County Medical Examiner Department were reviewed for the years 1972 through 1981. Any case in which acetaminophen was detected, regardless of cause of death, was included in the study. The reason for the performance of the analysis was usually determined by the circumstances surrounding the death. In some instances the test was specifically requested; in others the detection was incidental to a drug screen.

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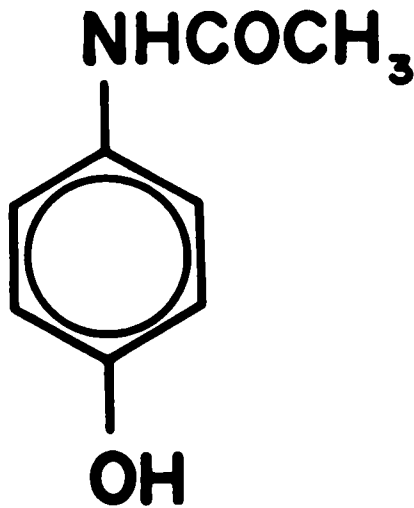


FIG. 1—Chemical composition of acetaminophen.

The detection method was ultraviolet spectrophotometry [2]. The result, when positive, was confirmed by the Walberg [3] method. The latter uses a trichloroacetic acid filtrate of serum to which sodium nitrite is added. A *nitro* compound was formed when acetaminophen was present. Ammonium sulfamate and sodium hydroxide were added and a yellow chromophore was formed. Absorbance was measured at 430 nm with a visible light spectrophotometer.

In 1972, 1891 autopsies were performed in Dade County, and 2837 in 1981. This was approximately a 50% increase in the number of autopsies over the ten-year study period. This increase in autopsy percentage exceeded the population increase, which was approximately 26%.

Results

Acetaminophen was detected in 95 cases (Fig. 2). In 1972 and 1973 there were no such cases. In 1974, there were four cases, and the number gradually rose over several years to a peak of 26 cases in 1978. In 1979 and 1980 there was a marked drop-off in the number of cases, but in 1981 the number rose to 18.

Of the 95 cases, 49 were females and 46 were males. There were 87 whites and 8 blacks. No predominant age group was evident among the cases detected (Fig. 3). Six cases were detected involving children under ten years old; these ranged in age from three months to three years. Five of these cases were natural deaths and the sixth was an accident caused by blunt force trauma. The paucity of cases in the second and ninth decades may be a reflection of the population autopsied.

Nearly two thirds of the positive cases had acetaminophen concentrations under the upper limit of the generally therapeutic range, 10 to 20 mg/L (Fig. 4). There were 17 cases with more than 50 mg/L. The highest serum concentration was 348 mg/L. Of the 17 cases with concentrations over 50 mg/L, 14 were drug overdoses caused by various combinations of drugs.

In 26 of the cases, Tylenol was the most common acetaminophen preparation used as opposed to 52 in which the brand name of the drug was unknown (Fig. 5). Information was sought by evaluation of the medications at the scene and by history. In nine cases, Darvocet-N was the drug preparation used. The known products used, in decreasing order of frequency, were Tylenol, Darvocet-N, and Tylenol with codeine.

In 69 of the 95 cases other drugs were associated with acetaminophen, either as part of a

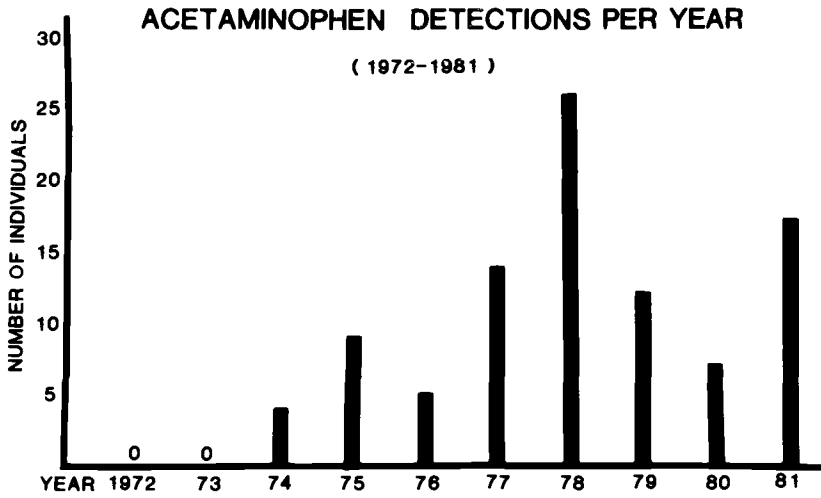


FIG. 2—Acetaminophen detections per year.

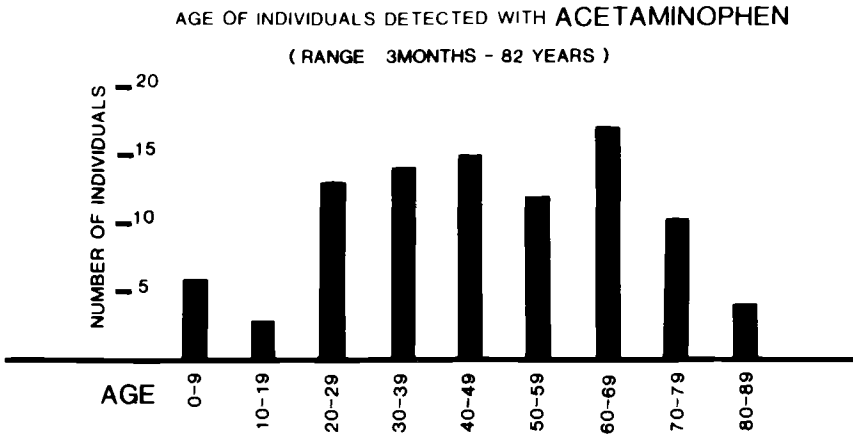


FIG. 3—Age of individuals in acetaminophen cases.

pharmaceutical preparation or as separate drugs. The most commonly associated drugs were barbiturates, ethanol, diazepam, salicylates, and propoxyphene (Fig. 6). In 26 of the 95 cases (27.4%) acetaminophen was the only drug. The manners of death in the 95 cases studied are listed in Fig. 7.

Propoxyphene was detected in 18 of 95 acetaminophen cases. Of these 18 cases, 12 were suicides and 2 were accidental overdoses. Darvocet-N was the source of the propoxyphene in 9 of the 18 cases.

In four cases in which death was caused by acetaminophen toxicity, the individuals were white females. Three had taken Tylenol and only one had taken acetaminophen in generic form. This last individual had the highest acetaminophen level, 348 mg/L. The other individuals had much lower acetaminophen levels, 130, 77, and 30 mg/L. Generally, toxic to lethal levels of acetaminophen are believed to be in the hundreds of milligrams per litre range.

Three of the four cases of lethal acetaminophen overdoses also had therapeutic doses of phenobarbital (Table 1). These four cases occurred between 1978 and 1981. Ages in these

INDIVIDUALS		DETECTED WITH <u>ACETAMINOPHEN</u>	
		(95 CASES)	
SEX		49 FEMALES	
		46 MALES	
RACE		87 WHITES (INCLUDING 2 INFANTS)	
		8 BLACKS (INCLUDING 4 INFANTS)	
		0-20	62 CASES
		22-50	16 CASES
LEVELS:	(MG:/L)	51-100	7 CASES
		101-200	8 CASES
		201-300	1 CASE
		300-400	1 CASE

FIG. 4—Acetaminophen levels and demographic distribution of cases.

**ACETAMINOPHEN PRODUCTS USED
(WHEN KNOWN)**

	NUMBERS OF CASES
TYLENOL	26
DARVOCET-N	9
TYLENOL WITH CODEINE	4
ACETAMINOPHEN(GENERIC)	2
PERCOCET	2
PARAFON FORTE	1
BANCAPS	1
NYQUIL	1
TYLOX	1

FIG. 5—Acetaminophen products used.

cases ranged from 31 to 72. Hospital survival was two to five days. Admission drug concentrations are listed in Table 1. The clinical synopses and liver findings of these four cases are as follows:

- Case I (79-3030) was a 65-year-old female found stuporous with a history of suicidal ingestion of 75 Tylenol. She survived about three-and-one-half days. The liver had a central zone of vacuolated fatty degeneration with coagulative necrosis surrounded by a nonfatty zone of coagulative necrosis. Only a thin zone of intact peripheral lobular cells remained. Admission blood drug concentration was 348 mg/L.
- Case II (78-2371) was a 31-year-old female epileptic with past episodes of drug overdoses and mental illness. She ingested approximately 85 Tylenol capsules. Subsequently she vomited. She survived five days. The liver had a diffuse uniform coagulative necrosis with only a few peripheral viable parenchymal cells, some with multiple nuclei. Fatty degeneration was absent. Admission blood drug concentrations were acetaminophen 30 mg/L and phenobarbital 37.2 mg/L.

**DRUGS FREQUENTLY ASSOCIATED WITH
ACETAMINOPHEN -NUMBER OF CASES IN
WHICH DETECTED**

BARBITURATES	22
ETHANOL	21
DIAZEPAM	21
SALICYLATES	19
PROPOXYPHENE	18
FLURAZEPAM	8

**26 OF 95 CASES (27.4%)-
NO ASSOCIATED DRUGS**

FIG. 6—Other drugs associated with acetaminophen cases.

MANNER OF DEATH (95 CASES)

	% OF TOTAL
40 SUICIDES (30 DUE TO VARIOUS DRUGS)	42.1%
30 NATURALS	31.6%
23 ACCIDENTS (10 DUE TO ACCIDENTAL OVERDOSE)	24.2%
2 HOMICIDES	2.1%
TOTAL 100%	

FIG. 7—Manner of death in 95 acetaminophen cases.

TABLE 1—Acetaminophen overdoses showing hepatic necrosis.

Case	Age	Sex	Admission Blood Level of Acetaminophen, mg/L	Days in Hospital	Other Drugs Involved	Manner of Death
I	65	female	348	3	none	suicide
II	31	female	30	5	phenytoin and phenobarbital	suicide
III	49	female	77	2	phenytoin, phenobar- bital, and mepro- bamate	suicide
IV	72	female	130	2.5	phenobarbital	accident

- Case III (81-1992) was a 49-year-old female found unconscious following a past history of mental illness and drug overdose. She survived two days. The liver had coagulative necrosis of the central third of the lobules, with sinusoidal congestion. Adjacent spared parenchymal cells had a scant fatty vacuolization of the cytoplasm. Admission blood drug concentrations were acetaminophen 77 mg/L, meprobamate 50 mg/L, phenytoin 7.6 mg/L, and phenobarbital 10.2 mg/L.

- Case IV (81-3145) was a 72-year-old female who ingested Tylenol and died four days later. She was a constant user of analgesics for hip joint pain. She also suffered an acute myocardial infarction. The liver had coagulative necrosis of the central third of the lobules, with some sinusoidal congestion. Fatty degeneration was not evident. Admission blood drug concentrations were acetaminophen 130.8 mg/L and phenobarbital 28.5 mg/L.

Suicides plus accidental deaths comprised approximately two thirds of the total 95 cases (Fig. 7), with 40 cases being directly attributable to overdose with a variety of drugs.

Discussion

Eighty percent of the cases were detected in the last five years of the ten-year period. No gradual year-to-year increase was evident. A peak was not apparent. It appears that increased advertising and resultant acetaminophen usage accounts for the increased detection. The sex distribution of the total group was not significant, and no age group was predominant.

Acetaminophen may be useful as a marker of a polydrug overdose. Of 17 cases where acetaminophen concentration exceeded 50 mg/L, 14 were polydrug overdoses. It should be noted that acetaminophen alone was detected in approximately a quarter of the cases.

There are two explanations of why three of the four lethal acetaminophen cases did not have extremely high concentrations of acetaminophen. First, there was a delay between ingestion and arrival at the hospital, so that the blood specimen obtained at the hospital may not represent the actual peak level. Second, all three of the individuals had taken phenobarbital along with the acetaminophen. Phenobarbital activates liver cytochrome P-450 enzymes [4]. These function as oxygen-activating enzymes, and drug oxidations produce toxic intermediate products from acetaminophen [5-7]. Enhancing these enzyme systems may potentiate the liver toxicity of acetaminophen. It is postulated that the centrilobular distribution of this necrosis is associated with the localization in the liver of the enzymes that metabolize the drug. It is the arylating metabolite of acetaminophen that is the toxic factor involved in producing the liver injury.

In England and Wales, with an estimated population of 50 million, acetaminophen (paracetamol) overdose deaths increased dramatically during the 1970s (Fig. 8) [8]. In 1971, there were 35 acetaminophen overdose deaths [9]; by 1978, the number had risen to 190 [10]. The experience in Dade County (1.7 million population at present) does not mirror that of the British. If the ratios of deaths were the same, Dade County should have had five to six deaths in 1978, which it did not. The reasons are not clear but may include usage, availability of other drugs of abuse, or ethnic variability. It is questionable whether reliable national statistics for acetaminophen overdose deaths in the United States are obtainable. A number of national agencies, as well as some of the individuals involved in acetaminophen studies, are unable to provide such information.

Why is acetaminophen being used by individuals for suicide? As a suicidal tool, acetaminophen is a poor choice, since the lethal hepatic necrosis takes several days to develop. One study [11] has shown that individuals take acetaminophen as a suicidal agent because of its easy availability. In this study, only 12 of the 107 queried to determine the motive for using acetaminophen (paracetamol) as a suicide tool were aware that acetaminophen causes hepatic damage. All twelve individuals, even with this knowledge, expected to become rapidly unconscious. All the individuals who were interviewed in this study said that if they had known that acetaminophen was not rapidly fatal, they would not have taken the drug.

ACETAMINOPHEN DEATHS (ENGLAND AND WALES)

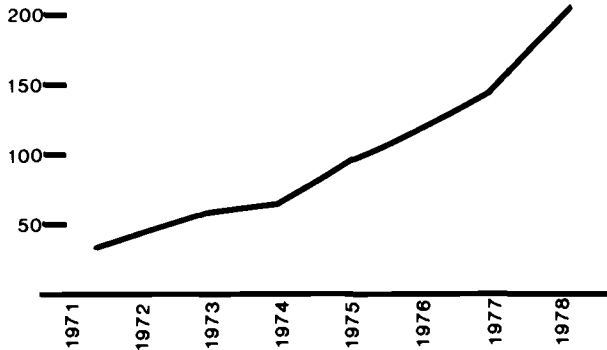


FIG. 8.—Acetaminophen deaths in England and Wales during the 1970s.

Our Dade County study reveals the following points: at the present time, the use and abuse of acetaminophen is not increasing on a regular year-to-year basis. There was an increase of use and abuse of this drug in the last five years of the study as opposed to the first five, but the number of individuals involved was not particularly large. One can only speculate whether this trend will change in the future with increased advertising and availability of acetaminophen. It would appear that advertising and over-the-counter availability of acetaminophen preparations are responsible for the increased use and concomitant abuse of the drug. In nearly three fourths of our cases, acetaminophen was associated with other drugs. Above a level of 50 mg/L of acetaminophen, the vast majority of cases were polydrug overdose deaths.

Postscript

Upon completion of this study, the deaths from ingestion of extra strength Tylenol capsules laced with cyanide were reported in Chicago. Whether these deaths will affect the future trend in the use and abuse of acetaminophen remains to be seen.

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