ACUTE INTOXICATION AND ILLNESS DUE TO MILD ANALGESICS

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- 1 Acute intoxication with mild analgesics is relatively uncommon in France. In fact, these drugs have accounted for only about 3.5% of acute drug intoxications seen at the Fernand Widal Hospital, Paris, over the past 10 years.
- 2 On the other hand, 23% of adverse reactions recorded by a drug monitoring service have been attributed to mild analgesics.
- 3 It is very difficult to establish the true incidence of acute toxicity and adverse reactions caused by these drugs. They are usually taken without medical supervision; it is often difficult to ascribe toxicity to a single agent when combination products are taken so frequently; and the underlying illness and the use of other drugs must also be considered.
- 4 The methods currently used to obtain adverse reaction and toxicity data have many disadvantages and shortcomings.

Introduction

THE low incidence of acute illness caused by analgesics is an important fact which is taken into account by legislative and regulatory bodies concerned with the safety and even necessity of certain drugs — be they traditional or new. Acute intoxication with mild analgesics may occur as a result of deliberate self-poisoning, and also following their therapeutic use. According to reports, both types of incident are relatively uncommon in France.

It is important to recognize the essential difference between information obtained from surveys and reports of adverse reactions following the therapeutic use of drugs given in the correct dosage for appropriate clinical indications, and toxicity resulting from overdosage and misuse of drugs. Unfortunately, this distinction is not always made. Clinical pharmacological and toxicological criteria may vary considerably from country to country and be interpreted quite differently by different regulatory and official bodies. Supplementary information on the safety of newer drugs may also be obtained during post-marketing surveillance and from preclinical toxicity studies in animals. In the final analysis, the facts must rest on clinical experience.

Frequency of acute intoxication and adverse reactions with mild analgesics

Patients with severe acute intoxication are usually seen in Accident and Emergency Departments and in

specialized Poisoning Treatment Units. In the Fernand Widal Hospital, Paris, about 1,000 cases are seen annually and over a period of 10 years mild analgesics have been involved on 328 (3.5%) occasions (Table 1).

Additional information can be obtained independently from the registration of calls to the Poison Centre. The number of calls increased from 12,000 in 1968 to 50,000 in 1979, but in the whole sample symptoms only occurred in 3% and severe toxicity in less than 0.5%. The true incidence is of course unknown because of incomplete reporting, and not all calls can be validated.

One year ago, however, we started a systematic screening programme to determine the side-effects and toxicity of glafenine based on clinical, toxicological and analytical data. So far, the incidence of oliguria and renal failure is running at one to four cases per month, mostly associated with high therapeutic doses. There have been three to five cases of urticaria and Quincke's oedema and zero to two cases of reversible shock monthly following the use of small doses. No deaths have been reported.

Data from a drug monitoring service revealed that 151 of 642 (23%) adverse effects were due to mild analgesics, and 50% of these were thought to have an allergic basis. Unfortunately, the mechanisms involved in adverse reactions often cannot be determined. Few centres have the necessary analytical and laboratory facilities for appropriate investigation and confirmation and in the case of suspected allergic reactions, re-challenge can be hazardous.

Table 1 Acute intoxication with mild analgesics in Emergency Unit, Fernand-Widal Hospital, Paris, 1968–1978

	<i>Certain</i>		<i>Probably associated with other drugs</i>		<i>Total</i>
	<i>Death</i>	<i>Survival</i>	<i>Death</i>	<i>Survival</i>	
Acetylsalicylic acid	0	40	1	50	91
Glafenine	0	30	0	38	68
Indomethacin	0	8	2	5	15
Paracetamol	3	2	0	7	12
Phenylbutazone	0	2	0	4	6
Phenacetin	0	4	0	0	4
Veganine*	0	16	0	30	46
Optalidon†	0	35	0	52	87

* Aspirin 250 mg, phenacetin 250 mg, codeine phosphate 10 mg.

† Aminophenazone 125 mg, caffeine 25 mg, butalbarbital 50 mg.

It is very difficult to establish the true incidence of acute toxicity and adverse reactions caused by mild analgesics. Most of these drugs are taken as self-medication without strict medical control or supervision, and the frequent use of combination products may make it difficult or impossible to ascribe toxicity to a single agent. The condition for which the analgesic was taken in the first place must be taken into account, not the least because other drugs might also have been involved. In some cases, a progressive increase in dose because of failure of relief of symptoms may lead gradually to intoxication. The apparent incidence of adverse reactions and toxicity of analgesics varies in different countries and this must be due in part to different patterns and habits of analgesic use and misuse. Some serious complications of the use of mild analgesics are summarised in Table 2.

Drug surveillance

Those responsible for collection of adverse reaction and toxicity data include (1) the staff of Poison Control Centres, (2) the official Drug Regulatory Agencies and (3) special hospital-based units for the local monitoring of adverse reactions. Some advantages and disadvantages of different methods of data collection are listed in Table 3. Further information comes from general practitioners and the scientific and medical literature, in which individual cases may be described in detail. Such publications come from widely scattered sources, and although they are of great importance, misleading conclusions can be drawn from isolated but dramatic case reports. It is important that unusual and rare reactions are assessed in relation to the medical and social context of their use. A few examples of specific toxicity often come to light within 5 years (usually within 2 or 3 years) of the marketing of a new drug. As drug-induced disease is often multifactorial, careful investigation of such cases is essential and

requires close cooperation between clinicians, regulatory agencies and the drug manufacturers. Many toxic reactions are very rare and the risk is so small that they do not constitute a public health problem unless the drug is used on a very large scale. In other cases, reactions may prove to be coincidental and unrelated to drug therapy.

These difficulties necessitate the classification of reports of drug toxicity encountered in routine clinical practice, epidemiological studies, and the compilation of a bibliography of adverse drug effects. Standard pharmacology and toxicology texts are of very limited value. Few give the necessary source references and there is rarely an indication of the frequency of adverse reactions in relation to the population at risk — a criticism which can also be levelled at many other publications.

At the end of the day, it is the sum of this limited

Table 2 Some serious complications of the use of mild analgesics recorded in the literature or seen at the Fernand Widal Hospital, Paris, 1968–1978

Aspirin	Gastrointestinal haemorrhage, asthma, acute allergic (anaphylactic) reactions, renal papillary necrosis, drug interactions
Glafenine	Acute allergic reactions (anaphylaxis), renal failure, hepatic damage, haemolytic anaemia
Paracetamol	Hepatitis, thrombocytopenia (rare)
Phenacetin (with other drugs)	Chronic renal failure, haemolytic anaemia, methaemoglobinaemia
Indomethacin	Gastrointestinal haemorrhage, ulceration and perforation. Haemolytic anaemia (rare)
Clomethacin	Hepatitis
Dextropropoxyphene	Respiratory depression, convulsions, hypoglycaemia (rare)

reference material which becomes the basis on which decisions such as the control and perhaps prohibition of a drug must be made by commissions and regulatory agencies who must advise and decide on the use of mild analgesics. It cannot be said that one drug is dangerous simply because it has caused at least one death any more than another drug can be said to be harmless because a million doses have been taken without obvious side-effects.

Severe illness and sequelae due to acute intoxication with mild analgesics are relatively infrequent because circulatory failure and acute renal and hepatic insufficiency can often be managed satisfactorily with modern techniques. However, the full resources of resuscitation and intensive medical care may be needed to prevent otherwise unavoidable death following acute poisoning. Subacute and chronic intoxication in patients with underlying pathology such as hepatic and renal disease might be avoided by more restrained and thoughtful prescribing and appropriate restriction of self medication with minor analgesics.

Conclusions

Deaths due to minor analgesics (following over-

dosage, self-poisoning, accidents, and serious acute reactions) are not numerous in France. Their frequency has been reduced in medically developed countries by improved emergency and intensive medical care. Serious toxicity is now better recognized through the work of Poison Control Centres, organizations for the monitoring and surveillance of adverse drug reactions, and the pharmaceutical manufacturers. The methodology for the study of drug reactions should include clinical observations, identification and estimation of drugs and their metabolites in blood and tissues, and investigation of possible predisposing factors, especially in the case of allergy.

Then comes the time for the detection and prevention of drug abuse. But this is another problem.

Editor's note: Although acute intoxication with mild analgesics does not seem to be an important problem in France, the position may be very different in other countries. In the UK, for example, these drugs account for about 25% of all cases of self-poisoning, with considerable morbidity and mortality.

Further reading

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Table 3 Limitations of methods to obtain information on toxicity and adverse drug reactions

	Advantages	Disadvantages
Recording of acute intoxication and acute side effects	Simple, cheap, data on most drugs, comparisons possible	Information must be obtained by comprehensive network of Poison Control Centres
Voluntary reporting to regulatory agencies	Simple in principle, cheap, all drugs and rare effects covered	Biased and incomplete reporting. Depends entirely on motivation of medical practitioners
Study of treated vs control patients (clinical trials)	Not expensive, frequency of specific reactions can be obtained	
Intensive drug monitoring in hospitals	Detailed studies of mechanisms possible. Interactions can be investigated. Frequency can be determined	Expensive, experience limited
Special studies — cohort and multicentre studies	Frequency and predisposing factors can be determined. All effects covered. High quality epidemiology	Very expensive. Information limited to one product. Time-consuming
Retrospective surveys of carcinogenicity and teratogenicity	Not very expensive	Depends on access to comprehensive medical records. Poor precision. Results are very late

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