MEDICAL PRACTICE

Contemporary Themes

Distalgesic poisoning—cause for concern

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Summary and conclusions

A review of all dextropropoxyphene poisoning episodes in a stable representative population during the past 10 years showed that Distalgesic accounts for most overdoses, and it has become an increasingly popular component of self-poisoning cocktails. Sudden respiratory depression due to dextropropoxyphene potentiated by other common ingested agents is the main danger, and at least one-third of patients take a potentially lethal dose (20 tablets of Distalgesic and alcohol or benzodiazepine). Naloxone is an effective antagonist but, because of the rapidity of deterioration, 40% of patients sustain irreversible cerebral damage before reaching resuscitation facilities. Consequently Distalgesic has become the ingested agent principally responsible for self-poisoning deaths over the age of 12 years. This rise to prominence has paralleled a pronounced increase in prescriptions for the drug. The reason for the increased rise in self-poisoning remains elusive. As effective treatment of the cause is not possible the only way to mitigate its serious consequences is prompt treatment and restrictions on the availability of the drug. No analgesics are devoid of danger in overdose, but in dextropropoxyphene the evidence suggests that its dangers outweigh its analgesic properties.

Introduction

Distalgesic, each tablet of which contains 32.5 mg dextropropoxyphene hydrochloride and 325 mg paracetamol, is by far the most commonly prescribed drug containing the synthetic opiate dextropropoxyphene. The immediate signs of overdosage are similar to those of morphine poisoning and are effectively reversed by naloxone.¹ Paracetamol is also a dangerous poison in overdosage, causing a potentially fatal hepatic necrosis¹ that is dose dependent. If recognised within 10 hours Distalgesic poisoning is treatable by the intravenous administration of precursors of glutathione, such as cysteamine (mercaptamine), L-methionine, and N-acetylcysteine.² Despite its obvious potential toxicity, reports of serious Distalgesic poisoning in Britain were sparse before 1977.^{3,4} At that time a coroner⁵ and two forensic pathologists⁶ published independent reports on 56 cases of fatal dextropropoxyphene poisoning encountered in their practices. It might have been expected that after these well-publicised reports the incidence of this poisoning would have fallen, while the availability of effective treatment would ensure the survival of those cases which occurred. This has not been our experience in hospital, however, and the previous studies^{5,6} suggested that additional deaths must be occurring in the community. The true epidemiology of this form of poisoning is unknown because an overall review has not been carried out. We hope that by presenting a comprehensive survey of dextropropoxyphene poisoning in a stable representative population we will fill this gap.

Hospital and methods

The acute medical unit for West Fife provides the district medical services for a relatively stable population of about 130 000. The clinical details of patients were recorded prospectively on to punched cards, which were then sorted by hand. Unconsciousness was graded according to the criteria of Matthew and Lawson.⁷ The basic prin-

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ciples of intensive supportive treatment⁸ were followed throughout. Data relating to deaths outside hospital were obtained from police records of sudden deaths.

Results

From January 1969 to June 1979, 82 patients (34 male, 48 female) were admitted with acute Distalgesic poisoning. Only four patients were admitted after taking dextropropoxyphene in any other form. The annual rate of admission is shown in the figure. Superimposed are the annual numbers of Scottish GP prescriptions for analgesics containing dextropropoxyphene (Scottish Home and Health Department data). The steady rise in incidence is not merely a function of the progressive increase in the proportion of such patients taking Distalgesic—this drug was implicated in 2% of cases of overdoses in 1971 and 7% by 1978. Distalgesic poisoning was commoner in the younger age groups, particularly below 25 years.

Annual number of Distalgesic poisoning cases admitted to hospital in West Fife and annual number of GP prescriptions for analgesics containing dextropropoxyphene in Scotland.

At the time of admission 20 patients had grade IV and two grade III coma; 12 had respiratory arrest, four severe epilepsy, three aspiration pneumonia, and one cardiac arrest; three patients died. All these serious complications were considered to be directly attributable to dextropropoxyphene and treated accordingly with naloxone and, where appropriate, assisted ventilation (15 needed endotracheal intubation).

Factors influencing the development of opiate complications in 82 patients with Distalgesic poisoning

	No of Distalgesic tablets		Associated ingestants	
	<20	≥20 or unknown	None or non-CNS depressant	CNS depressant†
No complications	30	29	26	32
Complications*	0	23	3	20

*Opiate complications as detailed in text.

†Alcohol (42), benzodiazepine (19), barbiturate (7), phenothiazine (2).

Twenty-three patients showed one or more of these toxic effects, as did one of the four who had taken dextropropoxyphene alone. By contrast, in only three cases was treatment required for toxic concentrations of paracetamol. Similarly, of 89 patients admitted during the same period because of paracetamol poisoning not associated with dextropropoxyphene, only five needed treatment with cysteamine or acetylcysteine, and there were no deaths.

The number of tablets containing dextropropoxyphene and the other central nervous system depressants and alcohol are shown in relation to the outcome in the table. This indicates that the incidence of serious toxic effects is related to dose and that sedatives or alcohol increase the dangers. There is a high risk of death if 20 or more Distalgesic tablets are taken with any other form of central nervous system depressant.

Police records of sudden deaths were available from January 1976. In the subsequent three and a half years there were nine deaths outside hospital from drug overdose—five due to Distalgesic and three to barbiturate—while in hospital there were four deaths from drug overdose, three being attributable to Distalgesic. Thus in the recent past most (8/13) deaths from drug overdose have been caused by Distalgesic and only a minority (3/13) by barbiturate. The deaths from Distalgesic were all people aged 30–60. Fifty-eight of the hospital admissions due to Distalgesic overdose occurred after January 1976, so that the overall death rate from this poisoning (1976–9) was 12.7% (8/63), in contrast with the death rate from all poisonings, which was 0.76%.⁹ Thirty-one (53%) patients were in the high-risk category (those who had taken 20 or more Distalgesic tablets with another central nervous system depressant), and this included all the fatalities, the death rate in this group being 25.8%. In 11 of these patients, however, respiratory arrest responded to prompt treatment with naloxone and mechanical ventilation. All would have died if they had not received early intensive medical care, and so the potential death rate in the high-risk group is about 60% (19/31).

Irrespective of the severity of poisoning, the proportion of patients assessed by consultant psychiatrists as needing further psychiatric treatment was almost identical—60% in those without complications and 56% in those with serious toxic effects. Six of the eight deaths occurred in recognised alcoholics, but in the remaining two cases there was no recorded psychiatric illness and the precipitating factor was marital disharmony.

Discussion

This study shows that even relatively modest overdose of Distalgesic is associated with high morbidity and mortality rates despite the availability of an effective antidote and good supportive treatment. These complications are almost entirely due to the opiate effects of dextropropoxyphene, particularly if these are potentiated by another respiratory depressant. The major problem is that severe respiratory failure and arrest may develop rapidly in circumstances where immediate medical facilities are not available. Distalgesic is becoming an increasingly popular constituent of self-poisoning mixtures. Overdoses now include more than one drug in at least one-third of cases, and the central nervous system depressants alcohol and benzodiazepines are often taken in combined poisonings.⁹ Not surprisingly in view of these recent trends, many patients with dextropropoxyphene poisoning come into the high-risk category because of the combination of drugs.

In our experience Distalgesic seems to have superseded barbiturates as the ingested agent principally responsible for deaths from self-poisoning and also as the drug that most often necessitates urgent resuscitation in poisoned patients.

The rising incidence of Distalgesic poisonings has followed remarkably closely the recent rise in the prescription rate for analgesics containing dextropropoxyphene. Previous evidence has indicated that poisoning trends reflect local prescribing habits¹⁰ and that most self-poisoned patients have taken prescribed drugs.¹¹ Furthermore, anecdotal evidence from patients and the police suggests that the hazards of Distalgesic and alcohol mixtures are now widely appreciated in the community, and this may well act as an incentive rather than a deterrent in some cases. Nevertheless, choice depends on availability.

Self-poisoning is endemic and increasing yet the precise explanation remains elusive.¹¹ Hence effective treatment of the cause is not possible in the immediate future and we can mitigate its more serious consequences only by prompt treatment and by restricting the availability of the potentially more dangerous drugs. No analgesics are devoid of dangers in overdose; but the dangers of dextropropoxyphene appear to outweigh its analgesic properties. With the additional hazard of dextropropoxyphene addiction,¹² the case against the continued widespread use of dextropropoxyphene seems overwhelming—particularly as the evidence suggests that no compound of dextropropoxyphene is likely to be superior to alternative and safer analgesics.¹³

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For Debate . . .

One cheer for Flowers?

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The students of King's College, London, ended their spirited reply to the Report of a Working Party on Medical and Dental Resources in the University of London (chairman Lord Flowers) with the thought from *Le Malade Imaginaire* that "Most men die of their remedies, not of their diseases," an apt rejoinder to Lord Flowers's quotation from Bacon that "No remedies cause so much pain as those which are efficacious." Truth has many sides: Molière perhaps puts therapeutics in a nutshell while Bacon might have a message for rationalisation. But, to continue with Molière, let me approach the matter in the spirit of *Le Misanthrope*, whose frankness was both his strength and his weakness and he paid for it with his friends. Let me be frank and not forfeit my London friends in the heat of the moment: forgive the pseudonym.

Background to change

In short, the background seems to be this: the London deans, the Medical Advisory Committee of the University, and the Department of Health saw a need for change. The deans feared that financial support for medical teaching in London would soon be insufficient to support all the medical and dental schools and postgraduate institutes as viable units. In response to this concern the vice-chancellor set up a working party to advise him. If the working party agreed that there was a problem (which it did) it was to suggest how medical education in London could best be reorganised to withstand the financial pressures, and if it considered it necessary to phase out one or more schools then it was to suggest which schools and when (which it has).

Now that the Flowers working party has courageously and uncomfortably reported, few schools and institutes seem to want anything to do with their recommendations. The Department of Health was at the same time concerned at the over-provision of hospital services in central London now that the population is moving out and appreciated that there were

implications for teaching. It asked the London Health Planning Consortium to advise it.

What is beautiful?

Argument in the university is essentially financial, academic, and pastoral. Pastoral fears were well expressed by the *Lancet*, which saw Flowers as a potential threat to "the integrity, corporate sense of purpose, and individually creative style of each school." Larger schools clearly run the risk of impersonality, but no one knows where the balance of advantage in size precisely lies. "Small is beautiful" is the general and understandable cry, but how small is both beautiful and best, and what is "beautiful" and what is "best"? Most agree that small is cosy, but the optimum size (or structure) of a preclinical school has never been defined. Clinical teaching in small groups around the patient is *not* challenged by Flowers: on that front he suggests only that students should be directed towards hospitals in the most populous areas.

Whether or not larger preclinical schools have solid economic virtues requires more facts than have yet been produced by either side, but is it really fair to argue that because British Steel and British Leyland are in a mess a preclinical school with an annual intake of 250 students will automatically be a disaster? Or, indeed, that because older buildings are cheaper to run new schools should close and old remain? London medical schools are the size they are largely by chance, not by scientific proof of either academic or financial optimum, while the concentration of hospitals in central London simply reflects demographic history.

The academic benefit which Lord Flowers sees in his working party's proposals seems to be part design and part a byproduct of the moves prompted by economic considerations. Each larger school would be able to develop a comprehensive range of departments equal to the changing emphasis of the course—departments large enough to be academically viable even if eroded by further financial cuts. Small, isolated post-graduate institutes would become exposed to the constructive

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