Consumption, overdose and death from analgesics during a period of over-the-counter availability of paracetamol in Denmark

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Abstract. Ott P, Dalhoff K, Hansen PB, Loft S, Poulsen HE (Department of Medicine A, Rigshospitalet, and Department of Pharmacology, Medical School, University of Copenhagen, Copenhagen, Denmark). Consumption, overdose and death from analgesics during a period of over-the-counter availability of paracetamol in Denmark. Journal of Internal Medicine 1990; 227: 423-428.

During the period 1978–1986, annual sales of paracetamol in Denmark increased from 1 million defined daily doses (DDD) (3 g) to 47 million DDD. While the number of admissions and deaths from overdose increased from 26 to 202 and from 1 to 3-4, respectively. The corresponding figures for salicylates are a decrease in sales from 113 to 94 million DDD, an increase in admissions from 282 to 595, and an increase in deaths from 5 to 22. From 1 January 1984 paracetamol became available on an over-the-counter basis. The figures for 1983 and 1984 were an increase in sales from 14 to 28 million DDD, an increase in admissions from 114 to 198, and an increase in deaths from 0 to 4. The number of deaths from opioid overdose remained constant at a value of about fifty during this period, the mortality per dose being about 20-fold higher than for paracetamol and salicylates. Dextropropoxyphene-related deaths increased twofold to 121 in 1986, with unchanged sales figures. A campaign launched by the National Board of Health resulted in a reduction in the number of deaths from dextropropoxyphene to 66 in 1987. The main effect of over-the-counter release of paracetamol was a dramatic increase in sales, without the epidemic of deaths observed a decade ago in the UK. It is suggested that the higher mortality of paracetamol poisonings in the UK compared to Denmark is related to the dextropropoxyphene content of the combination product, which is not available in Denmark. From an epidemiological toxicological viewpoint such combinations are not justified.

Keywords: acetaminophen, analgesics, drug regulation, paracetamol, self-poisoning.

Introduction

Self-poisoning with drugs is a common problem that accounts for a percentage of acute medical admissions that runs into two figures [1], many cases being due to overdose with analgesics. The problem is increasing, and one of the questions that it raises is whether self-poisoning with drugs is related to their availability. Denmark provides unique conditions for the study of this question, because the statistics of the National Board of Health cover all hospital admissions and causes of death, and all drug sales are registered by the Danish Drug Market Statistics. Furthermore, during the last decade salicylates have become available on an over-the-counter basis, and in 1984 paracetamol was changed from a prescription drug to an over-the-counter-drug.

Paracetamol (acetaminophen) has been documented since the last century [2] but its use has not increased until recent decades. Following massive overdose, fulminant hepatic failure is observed [3, 4], and in the UK and USA the number of deaths from paracetamol poisoning is considerable [4, 5]. The hepatotoxicity is believed to be caused by a toxic
metabolite [6], and can be prevented by the antidote N-acetyl cysteine [1, 5] if the latter is administered soon after the drug intake.

Using the Danish Drug Market Statistics (Dansk Lægemiddelstatistik) and the National Board of Health records as information sources, we have attempted to evaluate the effects of changes in paracetamol availability. For comparison, data were also collected for salicylates, dextropropoxyphene and opioid drugs, and for the total number of suicides.

Materials and methods

In Denmark, drugs are only sold from pharmacies, whether prescribed or over-the-counter. Drug consumption is monitored by the Danish Drug Market Statistics (Dansk Lægemiddelstatistik), which records all sales from merchant to pharmacy [7]. It was technically feasible to obtain data for the period 1978–1987 on sales of analgesic drugs categorized into four groups: (1) paracetamol; (2) salicylates alone or in combination; (3) dextropropoxyphene; and (4) opioids with the exception of dextropropoxyphene. For technical reasons phenazine, phenacetin and pentazocine could not be eliminated from group (2), although these compounds were quantitatively unimportant. The consumption was standardized to defined daily doses (DDD), which were as follows: 3 g for paracetamol and salicylates; 0.2 g for dextropropoxyphene; and variable for the remaining opioids.

All admissions from Danish hospitals together with the causes of all deaths are registered by the National Board of Health [8] according to the international WHO diagnosis classification system.

On the basis of the data available for the period 1979–1986, admissions and deaths after intoxication with analgesics were grouped into four categories corresponding to those of drug sale. For the paracetamol and salicylate groups, poisoning with these two drugs was recorded. The dextropropoxyphene group included intoxication with indo-methacin, phenacetin and phenprofen, but the latter three drugs were quantitatively unimportant. The importance of and number of deaths from overdose of illegal opioids cannot be determined accurately, but some estimates were available from the Council on Alcohol and Narcotics [9].

Results and discussion

The availability of paracetamol as an over-the-counter drug in Denmark from 1 January 1984 was followed by a doubling of sales. However, a steady increase in sales was apparent before 1984 and continued during the following years, as shown in Fig. 1. The increase in sales was accompanied by a relative decrease in the number of hospital admissions and deaths from paracetamol overdose (Figs 2 and 3). Consumption-related morbidity and mortality from paracetamol overdose showed a decrease (Tables 1 and 2). The 50-fold increase in paracetamol sales and the extended availability of the drug did not result in an epidemic of paracetamol-related deaths as might have been expected on the basis of the UK experience.

Salicylates were available over-the-counter throughout the study period. The sales of salicylates showed a minor decrease without notable changes in 1984, the year in which paracetamol became available.

Fig. 1. Sales of paracetamol, salicylates, dextropropoxyphene and opioids from pharmacies in Denmark during the period 1978–1987. The ordinate scale represents daily defined doses as described in materials and methods section. (-----) = paracetamol, (--) = opioids, (.....) = dextropropoxyphene, (----) = salicylates.
Fig. 2. Number of cases admitted to all Danish hospitals following overdoses with paracetamol, salicylates, dextropropoxyphene and opioids. The ordinate scale represents absolute values. For explanation of symbols see legend to Fig. 1.

Fig. 3. Number of deaths in Denmark following overdoses with paracetamol, salicylates, dextropropoxyphene and opioids. The ordinate scale represents absolute values. For explanation of symbols see legend to Fig. 1.

available as an over-the-counter drug. There was an increase in the number of hospitalizations and deaths after salicylates became available (Figs 2 and 3), resulting in an increase in consumption-related morbidity and mortality (Tables 1 and 2). Comparing salicylates and paracetamol, the same range of consumption-related morbidity and mortality was observed, but with opposite trends. This somewhat surprising result may be related to the fact that in 80% of formulations sold, salicylates are combined with codeine (10 mg) or sedative, while paracetamol is only available as a mono-component drug. However, this possibility was not supported by more detailed analysis of the sales data. Sales of mono-component salicylates during the period 1983–1987 decreased from 24.5 to 13.0 x 10^8 DDD per year, but there was also a decrease in the consumption of salicylate-codeine formulations from 83.7 to 80.5 x 10^8 DDD per year. From uncontrolled clinical observations an impression is gained of overconsumption of salicylate-codeine combinations in a small group of patients. Such a view cannot be verified by the present data.

Dextropropoxyphene and other opioids are only available by doctor’s prescription. The sales of dextropropoxyphene remained constant during the study period, while sales steadily increased for other opioids. The number of admissions to hospitals after opioid overdose and the mortality fluctuated somewhat during this period, but without relation to sales. In the case of dextropropoxyphene, however, a doubling of admissions occurred during the study period, and there was a twofold increase in consumption-related mortality. Poisoning related to illegal drug abuse might increase opioid and dextropropoxyphene morbidity and mortality. According
Table 1. Consumption related morbidity of analgesic drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Paracetamol</th>
<th>Salicylates</th>
<th>Dextropropoxyphene</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>11.6</td>
<td>2.4</td>
<td>27.7</td>
<td>67.2</td>
</tr>
<tr>
<td>1980</td>
<td>9.4</td>
<td>4.2</td>
<td>29.6</td>
<td>96.6</td>
</tr>
<tr>
<td>1981</td>
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<td>4.2</td>
<td>25.9</td>
<td>97.3</td>
</tr>
<tr>
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<td>8.6</td>
<td>4.1</td>
<td>24.9</td>
<td>84.5</td>
</tr>
<tr>
<td>1983</td>
<td>8.4</td>
<td>4.3</td>
<td>25.9</td>
<td>67.6</td>
</tr>
<tr>
<td>1984</td>
<td>7.1</td>
<td>5.6</td>
<td>28.9</td>
<td>49.4</td>
</tr>
<tr>
<td>1985</td>
<td>6.4</td>
<td>5.5</td>
<td>26.1</td>
<td>50.1</td>
</tr>
<tr>
<td>1986</td>
<td>5.0</td>
<td>6.1</td>
<td>34.3</td>
<td>25.5</td>
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</tbody>
</table>

Table 2. Consumption related mortality of analgesic drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Paracetamol</th>
<th>Salicylates</th>
<th>Dextropropoxyphene</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
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<td>0.04</td>
<td>4.9</td>
<td>9.5</td>
</tr>
<tr>
<td>1980</td>
<td>0</td>
<td>0.04</td>
<td>4.7</td>
<td>13.5</td>
</tr>
<tr>
<td>1981</td>
<td>0</td>
<td>0.05</td>
<td>5.1</td>
<td>13.0</td>
</tr>
<tr>
<td>1982</td>
<td>0.10</td>
<td>0.08</td>
<td>5.6</td>
<td>7.1</td>
</tr>
<tr>
<td>1983</td>
<td>0</td>
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<td>5.6</td>
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</tr>
<tr>
<td>1984</td>
<td>0.14</td>
<td>0.11</td>
<td>5.1</td>
<td>5.5</td>
</tr>
<tr>
<td>1985</td>
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<tr>
<td>1986</td>
<td>0.07</td>
<td>0.23</td>
<td>8.2</td>
<td>4.9</td>
</tr>
</tbody>
</table>

to estimates by the Council on Alcohol and Narcotics [9], about $2 \times 10^4$ DDD of opioids, mainly heroin, was illegally imported in 1985, and 150 deaths were related to such drug abuse (I. S. Kristensen, personal communication). Such deaths are normally registered by the police rather than by hospitals, and are not reflected in the National Board of Health’s records as related to analgesics. However, from the death certificates in the present study it was estimated that drug addicts represented 62% (range 45–78%) of opioid deaths and 10% (range 4–14%) of dextropropoxyphene deaths. In 1986, consumption-related mortality of dextropropoxyphene was about 60% higher than that of opioids. In view of the fact that bias from illegal drugs was strongest in the opioid group, conventional medical use of dextropropoxyphene appeared to be even more hazardous than that of opioids. This development prompted the National Board of Health to launch a campaign in the Danish medical journal [10, 11] and general newspapers, resulting in a halving of the number of dextropropoxyphene-related deaths (Fig. 3) between 1986 and 1987. As an additional safety measure, dextropropoxyphene is now only available by special prescription, a copy of which is sent to the National Board for post-marketing surveillance (since mid-1988).

Throughout the period investigated, suicides ranged from 1318–1617 per year and deaths after drug overdose ranged from 595–718 per year, without any clear trends (Fig. 4). Deaths from analgesic poisoning increased steadily from 97 in 1979 to 199 in 1986. It is therefore more likely that the observed trends for analgesics are due to the changed availability of the drug than to a general change in the society in this respect. It is significant that an increase or decrease in drug-related deaths such as those described in this paper is not reflected in such general statistics which can only detect large overall trends.

The difference between the incidence of paracetamol poisoning in Denmark reported here and records from the UK and USA [12–15] is striking. In the UK, paracetamol alone or in combination with
dextropropoxyphene was responsible for 8.5 deaths per million inhabitants per year during the period 1976–1984 [15], and 9.7 deaths per million inhabitants in 1984 [16]. In Denmark, 0.6 deaths per million inhabitants from paracetamol overdose were recorded after the initiation of over-the-counter availability in 1984. We have had no access to the UK sales figures, but it appears unlikely that paracetamol sales would be sevenfold higher in the UK. The combination of dextropropoxyphene and paracetamol is available in the UK, and was implicated in the majority of paracetamol poisonings there, a circumstance that attracted special attention. In Denmark this combination is not available. It is therefore possible that the higher mortality of paracetamol overdose in the UK is related to the concomitant unavoidable dextropropoxyphene overdose from the combined formulation. A synergistic effect of dextropropoxyphene on paracetamol toxicity is a possibility that cannot be confirmed on the basis of the present study, or from observations in the UK [16–18].

Morbidity and mortality from overdose with the minor analgesics paracetamol and salicylates correlate closely, the paracetamol profile appearing to be somewhat more favourable. This was not significantly affected by changing to over-the-counter availability of paracetamol. Compared to the minor analgesics, the morbidity and mortality of overdose with dextropropoxyphene and narcotics are 5–7-fold to 20-fold higher. Combinations of minor analgesics and dextropropoxyphene or narcotics presumably result in an increase in the number of deaths that occur due to suicidal overdoses. From an epidemiological-toxicological viewpoint such combinations are not justified.

References


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