Worldwide Variation in Chloramphenicol Utilization: Should It Cause Concern?

C. R. Kumana, BSc, FRCP, K. Y. Li, DipPharm, and P. Y. Chau, MB, FRCPath

Per capita sales of chloramphenicol in Hong Kong (which presumably reflect adult and pediatric consumption in the community) are between about 11 to 44 fold greater than in several western countries and Australia. Despite such relatively excessive exposure to a potentially marrow-damaging drug, the certified death rate from aplastic anemia in Hong Kong was only 0.4 per 1000 deaths compared with 1.0 per 1000 in England and Wales. Nor was there any other evidence to indicate that Hong Kong residents suffered an excessive incidence of aplastic anemia. Wherever chloramphenicol use is widespread, prospective investigations should be undertaken in the local population to evaluate the alleged high risks of producing aplastic anemia.

Chloramphenicol induced aplastic anemia is usually fatal, not dose dependent but idiosyncratic (cases have been reported following single doses), presents after 5 to >270 days and has an estimated risk of about 1/50,000 to 1/20,000 of those exposed.1-4 Consequently, in many countries chloramphenicol therapy is restricted to a limited number of indications, such as typhoid fever and Haemophilus influenza meningitis. Under the circumstances, we were surprised by the very large amounts sold in Hong Kong (both for adults and children), particularly as antimicrobials are prescription drugs. Moreover, chloramphenicol is not permitted for veterinary use or animal husbandry and government testing confirms local meat supplies, poultry and fish contain virtually no traces of the drug (personal communication).

METHODS

Importers and local manufacturers of drugs in Hong Kong, must hold product registration certificates for each item and for important items such as antimicrobials they are required to keep complete sales statistics for a limited period of time. Chloramphenicol registration certificate holders were identified (41 in all), contacted by Medical and Health Department pharmacists and asked to provide relevant sales statistics. Comparative data on chloramphenicol use in other countries (whether based on sales or prescriptions) was obtained from published literature and by corresponding with appropriate government agencies.

Because of the vast amounts of chloramphenicol being sold in Hong Kong, we were anxious to discover to what extent it might contribute to the local incidence of aplastic anemia. However, most of our patients remain unaware of the drugs they take. Moreover, as chloramphenicol induced aplastic anemia usually presents many months and possibly up to 1 year after exposure, recall of drug exposure may be vague. Thus, most cases may never be identified as such. We therefore set out to determine, whether there might be a relatively high incidence of aplastic anemia in Hong Kong (regardless of identifiable cause), compared with countries where chloramphenicol sales were minimal. Accordingly, we used various sources including death certification records, to provide information regarding the incidence of aplastic anemia in Hong Kong and elsewhere.

RESULTS

Chloramphenicol Sales/Prescribing

Table I shows that the vast majority of chloramphenicol sales in Hong Kong were to retail pharmacists and individual practitioners. Major govern-
cation records for the territory (over the period 1981–85 inclusive) showed an average annual death rate from aplastic anemia of 0.4/1000 deaths, compared with 1.0/1000 deaths in the England and Wales. Nor are Hong Kong hematologists aware of a large excess of aplastic anemia patients. Thus, Queen Mary Hospital (which deals with >50% of the territory’s serious hematological cases) encountered only six new cases of aplastic anemia in 1985, none of which were linked to chloramphenicol exposure. In several European countries and Israel, the incidence of aplastic anemia was reported to range from 0.6 to 3.1/million/year, but the extent of chloramphenicol exposure was not commented on.

**DISCUSSION**

The aetiology of chloramphenicol induced aplastic anemia has been extensively reviewed and may depend on one or more of the following: formation of toxic metabolites, route of administration, genetic susceptibility, prior bone marrow damage. The observation that aplastic anemia scarcely ever ensued if chloramphenicol administration was confined to the parenteral route, may be explained by the rarity of exclusively parenteral dosing. According to an alternative suggestion, prior to entering the body non-parenteral chloramphenicol may occasionally be converted into toxic metabolites by gastrointestinal or other superficial bacteria, thus accounting for the apparent safety of parenteral dosing.

The amounts of chloramphenicol sold in Hong Kong are astounding when compared with those from several other developed nations (Table III); average per capita sales being about 442—22 fold greater than in the nations listed. Chloramphenicol use in Nordic countries (Table IV) was collected as part of a coordinated endeavor to obtain complete

**TABLE I**

<table>
<thead>
<tr>
<th>Average Monthly Sales of Chloramphenicol in Hong Kong (January 84–June 85 inclusive)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tables/Capsules (Adult Use)</td>
</tr>
<tr>
<td>Liquid formulations (Paediatric use)</td>
</tr>
<tr>
<td>Parenteral Preparations</td>
</tr>
<tr>
<td>Tablets/Capsules</td>
</tr>
</tbody>
</table>

*Information supplied courtesy of Medical and Health Department, Hong Kong.

**TABLE II**

<table>
<thead>
<tr>
<th>Chloramphenicol Use in 15 Countries, 1983</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined Daily Doses/1000 Population</td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>North &amp; South America</td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>United States</td>
</tr>
<tr>
<td>Mexico</td>
</tr>
<tr>
<td>Brazil</td>
</tr>
<tr>
<td>Argentina</td>
</tr>
<tr>
<td>Venezuela</td>
</tr>
</tbody>
</table>

Modified from Table 6 S239, Estimates of Antibiotic Usage, Col and O’Connor (1987). Note: Defined daily dose of chloramphenicol = 3 G.
VARIABILITY OF CHLORAMPHENICOL UTILIZATION

TABLE III

Chloramphenicol Prescribing/Sales for Human Consumption

<table>
<thead>
<tr>
<th>Country or Territory</th>
<th>Population</th>
<th>Average Monthly Sales in Grams</th>
<th>Tablets and Capsules (Liquid)</th>
<th>Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>based on January 1984– June 1985</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>55 million</td>
<td>102,078</td>
<td>(30,544)</td>
<td>2652</td>
</tr>
<tr>
<td>Canada</td>
<td>25 million</td>
<td>1982</td>
<td>1983</td>
<td>1984</td>
</tr>
<tr>
<td>Australia</td>
<td>15 million</td>
<td>6</td>
<td>22</td>
<td>123</td>
</tr>
<tr>
<td>Sweden</td>
<td>8 million</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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* Estimate based on a survey of retail pharmacy prescriptions (excluding dispensing by doctors and hospitals)
* Courtesy Health Protection Branch, Health and Welfare Canada. Data refers to total sales by manufacturers and wholesalers.
* Courtesy Commonwealth Department of Health, Canberra. Data refers to prescribing under the Australian Pharmaceutical Benefits Scheme.
* Data obtained from Swedish Drug Information System Databank (SWEDIS)

statistics on drug sales using similar sources (whole-
sale stage). The figures for each country are there-
fore comprehensive, comparable to each other, and
because of the way in which they were derived they
also bear comparison with those from Hong Kong.
On this basis, the per capita 1984/85 Hong Kong
sales were approximately 11 to 29 fold greater than
the average 1981–83 sales in Nordic countries.
Among the countries listed in Table II, only the per
capita sales from Argentina and Spain exceeded
those from Hong Kong. Due to the diverse sources
from which the sales data in our tables was com-
piled, the figures from different countries may not
be strictly comparable to each other, and small in-
accuracies and inconsistencies were only to be ex-
pected. For example, the 1983 chloramphenicol

TABLE IV

Chloramphenicol Sales in Nordic Countries

<table>
<thead>
<tr>
<th></th>
<th>Denmark</th>
<th>Finland</th>
<th>Iceland</th>
<th>Norway</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grams sold</td>
<td>1981</td>
<td>0.03</td>
<td>0.03</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>1000 inhabits</td>
<td>1982</td>
<td>0.03</td>
<td>0.03</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>Per day</td>
<td>1983</td>
<td>0.06</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adapted from Nordic Statistics on medicines (3), referring to rounded off figures for Defined Daily Doses (DDDs); and assuming that 1 DDD of chloramphenicol = 3 G.

sales for Sweden reported by the Nordic Council of
Medicines (Table IV) amounted to 0.03 G/1000 in-
habitants/day compared to 0.04 G/1000 inhabi-
tants/day obtained from SWEDIS (Table III). How-
ever, the scale of difference between Hong Kong
sales and those in developed countries are strongly
indicative of genuine differences in use. We also ap-
preciate that by no means all drugs sold (or pre-
scribed) are consumed. Nevertheless, in the absence
of supervised drug administration, only sales/pre-
scription data can provide a means of estimating use
and enable albeit indirect and imperfect compar-
isons.

The vast amounts of chloramphenicol sold in
Hong Kong, were unlikely to be accounted for by the
incidence of typhoid fever, Hemophilus influenza
meningitis or other serious infections for which chloramphenicol is particularly warranted. Thus, according to Hong Kong Government statistics over the last five years, the average number of typhoid and paratyphoid cases notified annually was 376. More likely, chloramphenicol was being prescribed for relatively common, less severe conditions, such as upper respiratory infections. Thus, assuming that on average 100,000 G were being prescribed per month as 5 G courses (250 mg four times daily for 5 days), about 240,000 courses were being taken annually. The actual number of persons exposed might be greater or smaller (average chloramphenicol courses could be smaller or larger, and a few individuals might be given multiple courses). On the basis that between one in 20,000 and one in 50,000 of those exposed develop aplastic anaemia, about 12-5 such cases might be expected in Hong Kong per year. Using a smaller (less conservative) estimate of the average course, for example 4 G as determined in a survey of out of hospital prescribing in the U.S.\textsuperscript{10} the anticipated numbers of patients exposed and the aplastic anemia cases expected would be correspondingly greater.

Possible reasons why an excessive incidence of aplastic anemia has not been recognized in Hong Kong despite the prevailing rate of chloramphenicol sales in the community, include:

a) Non diagnosis and inaccurate death certification: This seems unlikely as such cases would be admitted to hospital and have their diagnosis confirmed by bone marrow examination. In Hong Kong referral to a tertiary facility and recourse to appropriate bone marrow biopsies is routine for patients with severe unexplained anemia or pancytopenia, whereas in other parts of the world this may not be the usual practice.\textsuperscript{6} Moreover, as Hong Kong is a British territory, where death certification procedures and practices are modeled on those of the U.K., a comparison of respective death certification records is particularly apt.

b) The inability to appreciate 2-3 extra cases of non-fatal aplastic anemia/year per major hospital: However, even after retrieving cases from a computerized record system used in our hospital no such trend was evident.

c) Less proneness to chloramphenicol induced aplastic anemia in the local population: Genetic factors are evidently important determinants of susceptibility.\textsuperscript{3,4} There is even speculation that, longstanding widespread chloramphenicol prescribing may have eliminated the genes conferring susceptibility to aplastic anaemia through natural selection. Alternatively, if bacterial metabolites are important in the pathogenesis of aplastic anaemia, inter-ethnic differences in the flora of the gut and other superficial surfaces could be clinically significant.

d) Other possible chloramphenicol related lethal pathology (e.g. Leukaemia) developing prior to aplastic anaemia: Though no such lethal disease has been well documented hitherto, at least one case control study claims to support an association between chloramphenicol use and childhood leukaemia.\textsuperscript{11}

e) Contrary to earlier views, most instances of irreversible aplastic anemia could be related to the dose and duration of chloramphenicol therapy.\textsuperscript{12} Thus, short courses with low doses (which presumably prevail in Hong Kong) may have less risk.

f) Risks of developing chloramphenicol induced aplastic anemia accepted hitherto might be exaggerated.

It is incontrovertible that chloramphenicol sales per capita in Hong Kong are several orders of magnitude greater than in many western countries and Australia. It is also likely that these differences reflect genuine differences in prescribing attitudes by doctors and the amounts being consumed by pa-

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**TABLE V**

<table>
<thead>
<tr>
<th>Resistance of Important Bacterial Pathogens (isolated in 1986 at the Queen Mary Hospital, Hong Kong) to Common Antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Isolates Resistant to</td>
</tr>
<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Hemophilus influenza</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Salmonella typhi and paratyphi</td>
</tr>
</tbody>
</table>

N/A = not applicable. Data provided courtesy of Microbiology Department, University of Hong Kong, Queen Mary Hospital.
tients. However, the extent to which such widespread chloramphenicol consumption contributes to aplastic anemia in the community appears to be much lower than anticipated. In many developing countries, chloramphenicol is widely regarded as a cheap and useful drug for the treatment of typhoid fever, meningitis and other serious infections (Table V), but the alleged high risks of aplastic anaemia remains a worry feature. In view of our findings, prospective investigations are urgently warranted to re-evaluate these risks, wherever widespread use of chloramphenicol continues. Only then, will it be possible to gauge its true value in the context of overall benefits and risks.

We thank Professor TK Chan for encouragement and useful discussion and helping to trace and confirm all new cases of aplastic anemia diagnosed in Queen Mary Hospital in 1985. We also thank Mr. N. Li (Senior Information Officer with the Hong Kong Medical and Health department) who provided statistics on aplastic anemia death certification.

REFERENCES