Side Effects of Non-Narcotic Analgesics as a Determinant of Prescribing

Olli S. Miettinen

Department of Epidemiology and Biostatistics, Department of Medicine, and Centre for Advanced Studies in the Theory and Practice of Medicine, McGill University, Montreal

Summary

In the prescription of non-narcotic analgesics the physician's main responsibility is to make sure that the quality-of-life improvement expected from the drug's use justifies the associated risk, low though it is, of fatal side effects. The range of acceptable risk depends, naturally, on the dosage and duration of the treatment and on those characteristics of the patient which bear on the drug's efficacy and safety. In the treatment of acute pain an additional, very important, factor is the patient's remaining life expectancy. Quantification of maximal acceptable risks is aided by formal decision-analytic considerations. Such analyses indicate that maximal acceptable risks vary by several orders of magnitude among various clinical situations and that they are more liberal than intuition might generally suggest.

The use of non-narcotic analgesics (NNAs), while a source of enormous health benefit to people everywhere, represents a health problem as well. In essence the problem is one of serious adverse reactions such as massive gastrointestinal haemorrhage or aplastic anaemia. Even though the risk (probability) of such a reaction occurring in any given user of an NNA is very low, the widespread use of these drugs means that an appreciable number of such cases do occur annually in any given country.

1. Quality versus Quantity of Life

The public health problem with NNA use in the population has to do more with the risks associated with individual courses of treatment than with the frequency of their use and their availability. It is important that the pattern of use of NNAs is such that the associated risks are justifiable by the benefits derived. The intended effect of an analgesic is to enhance the quality of life. For analgesic treatment to be justified the patient's quality of life without pain, or drug-induced alleviation of pain, along with whatever symptomatic side effects may result from treatment, must be preferable to the quality with the untreated pain. If the analgesic is completely safe, in that it is free of life-threatening side effects, the positive effect on the quality of life justifies its use. On the other hand, if the drug has any potential for life-threatening adverse reactions, the prescriber must decide whether to use the drug or to select a possibly less effective, though safer, alternative. In order to make such a decision it is necessary to offset improvement in quality of life against any potential decrease in the duration of life.
Given the possibility of an adverse drug reaction being fatal, the justifiable risk can be defined as the risk that an informed individual is willing to take once he or she is also made aware of the benefit, or as the risk an individual with a particular disease or experiencing a certain loss of quality of life should be prepared to take, given the benefits.

2. Treatment of Chronic Pain

As an example of the decision whether or not to prescribe analgesics, consider their use for chronic, life-long pain, such as that of arthritis. To derive a mathematical equation to determine the acceptable level of reduction in duration of life, let $1 - Q_0$ denote severity of pain, $1 - Q_1$ the residual pain plus symptomatic side effects (with $Q_1 > Q_0$) and $S_1$ the fractional shortening of life resulting from the fatal side effects of the treatment. The equation $S_1 < 1 - Q_0/Q_1$ defines the acceptable level of the decrease in quality-adjusted duration of life.

For example, if untreated arthritis pain reduces the quality of life by 30% ($Q_0 = 70\%$) and if the residual pain plus the symptomatic side effects reduce it by 10% ($Q_1 = 90\%$), then an acceptable analgesic medication, lasting for the rest of life, can reduce the duration of life by less than $1 - 70/90 = 22\%$. This bound is actually too high, since it presupposes that there is no chance of improving the situation, whereas it is reasonable to expect that safer alternative drugs will become available in the course of the treatment.

3. Treatment of Acute Pain

The justifiable risk of analgesic will vary greatly according to the loss of quality of life due to pain, the efficacy of treatment, the duration of pain if untreated and the life expectancy of the patient. The influence of these factors on justifiable risk of a fatal adverse reaction to an NNA is illustrated in table I, where the duration of pain is 1 or 5 days and the remaining life expectancy is 30 or 60 years. The latter is examined below. By using the equation in table I, it can be seen that the justifiable risk is several magnitudes less in young patients whose pain minimally reduces quality of life than in older patients whose quality of life is greatly reduced by their pain.

Thus, for each NNA prescribed, the level of acceptable risk will depend on the type of indication (e.g. headache, cancer pain), the age of the patient and their disease, and the dose and duration of treatment necessary to achieve a satisfactory improvement in the quality of life.

4. The Drug of Choice

When more than one analgesic satisfies the acceptable-risk criterion it is important that the prescriber identify the analgesic of choice for each patient. This involves, first, as any intervention decision does, consideration of the patient's personal conception of relative importance of quality and quantity of life (to define $Q_0$ and $Q_1$) and the expected duration of the treatment in his/her particular case; and it involves the drug-specific fatality risks and relative efficacy of available analgesics in patients of the sort that he or she represents. Ascertaining these particulars for a particular patient can represent quite a challenge for the physician and thus constitutes a good justification for the regulatory requirement that the choice of analgesic in the context of appreciable risks should involve the professionalism of the prescribing physician.

### Table I. Examples of justifiable risk of fatal adverse drug reaction to a non-narcotic analgesic according to patient characteristics and efficacy of treatment

<table>
<thead>
<tr>
<th>Loss of quality of life due to pain (A)</th>
<th>50% (n = 0.5)</th>
<th>5% (n = 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of treatment (B)</td>
<td>100% (n = 1)</td>
<td>50% (n = 0.5)</td>
</tr>
<tr>
<td>Duration of pain (C) [days]</td>
<td>5/365</td>
<td>1/365</td>
</tr>
<tr>
<td>Remaining life expectancy (D) [years]</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Justifiable risk* (E)</td>
<td>1/5000</td>
<td>1/1,000,000</td>
</tr>
</tbody>
</table>

*a Justifiable risk (E) = A x B x C + D.