Non-steroidal Anti-inflammatory Drugs Ranking by Nondeterministic Assessments of Probabilistic Type

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Abstract

With a number of common therapeutic prescriptions, common mechanisms, common pharmacological effects - analgesic, antipyretic and anti-inflammatory (acetaminophen excepted), common side effects (SE) (platelet dysfunction, gastritis and peptic ulcers, renal insufficiency in susceptible patients, water and sodium retention, edemas, nephropathies), and only a few different characteristics - different chemical structures, pharmacokinetics and different therapeutic possibility, different selectivities according to cyclooxygenase pathway 1 and 2, non-steroidal anti-inflammatory drugs (NSAIDs) similarities are more apparent than differences. Being known that in a correct treatment benefits would exceed risks, the question “Which anti-inflammatory drug presents the lowest risks for a patient?” is just natural. By the Global Risk Method (GRM) and the Maximum Risk Method (MRM) we have determined the ranking of fourteen NSAIDs considering the risks presented by each particular NSAID. Nimesulide, Etoricoxib and Celecoxib safety level came superior to the other NSAIDs, whereas Etodolac and Indomethacin present an increased side effects risk.

Keywords: NSAIDs ranking; NSAIDs side effects (SE); Ranking methods; Global Risk Method; Maximum Risk Method

Introduction

Non-steroidal Anti-inflammatory Drugs (NSAIDs) have three major effects: antipyretic, analgesic and anti-inflammatory (acetaminophen excepted), and have other effects considered secondary: inhibition of uterine contractions (tocolytic effect), the effect of closing the persistent ductus arteriosus in neonates (indomethacin), decreased intestinal peristalsis, reduced risk of certain types of cancer (colorectal cancer, breast cancer - celecoxib), antiplatelet effect (cardiology dose aspirin 75-325 mg/day, indomethacin, phenylbutazone) and each of them are not equally potent in these actions [1]. NSAIDs also share the same side effects: cutaneous [2,3], hepatic [4-6], renal [7-10], gastrointestinal [11-14], musculoskeletal SE [4,15], cardiovascular [4, 16-19], respiratory, urinary, nervous [4].

NSAID ranking according to their implied risk is extremely useful, representing an evaluation of the same according to their possible impact on the patient. Side effects of drugs are gathered according to six categories [20]: dose-dependent, dose-independent, administration-time-dependent, dose-dependent and administration-time-dependent, abandon (giving up treatment because of side
effects) and treatment failure (because of inefficiency). In this article we determined a NSAID ranking considering risk-type criteria.

Material and Method

We have considered the following fourteen non-steroidal anti-inflammatory drugs (random order): Celecoxib, Ibuprofen, Naproxen, Etoricoxib, Diclofenac, Ketoprofen, Indomethacin, Nimesulide, Piroxicam, Meloxicam, Acetaminophen, Ketorolac, Etodolac, Tenoxicam.

In order to gather all the relevant information we have used meta-analysis type studies or original articles selected by means of MEDLINE search engine based on key words (non-steroidal anti-inflammatory drugs, side effects, efficiency, gastrointestinal side effects, cardiovascular side effects, nephrotoxicity, hepatotoxicity, cutaneous side effects, musculoskeletal side effects, Celecoxib, Ibuprofen, Naproxen, Etoricoxib, Diclofenac, Ketoprofen, Indomethacin, Nimesulide, Piroxicam, Meloxicam, Acetaminophen, Ketorolac, Etodolac, Tenoxicam). Finally we have selected those studies containing information related to the number of patients include in the survey and the number of side effects generated by the administration of a NSAID [4, 16-19, 21-65].

We have used the risk-type criteria, representing the probability that the patient may develop a side effect (SE): cutaneous, gastrointestinal, hepatic, respiratory, renal, urinary, cardiovascular, nervous, musculoskeletal, severe cardiovascular risk (myocardial infarction, stroke and sudden cardiac death), treatment failure (inefficiency) and abandon.

The ranking complexity increases as soon as several ranking options appear, depending on a great number of criteria that may be in conflict, at the same time increasing the number and the nature of uncertainty factors. Criteria are separately assessed and they must be independent from one another.

Applying the independence algorithm based on the Pearson correlations we have obtained the following criteria: cutaneous SE, gastrointestinal SE, hepatic SE, respiratory, renal, urinary, cardiovascular SE, nervous SE, musculoskeletal SE, severe cardiovascular risk and Inefficiency.

Global Risk Method (GRM)

An assessment of each NSAID is displayed below by estimating risk probability for one of A1,A2,..., An ailments presumed independent. Therefore, for each NSAID, the risk to develop at least one of A1,A2,..., An ailments is assessed according to the following formula:

\[
F(NSAIDs) = \Pr(A_1 \cup A_2 \cup \ldots \cup A_n)
\]

where

\[
\Pr(A_1 \cup A_2 \cup \ldots \cup A_n) = \sum_{i=1}^{n} \Pr(A_i) - \sum_{i<j}^{n} \Pr(A_i \cap A_j) + \sum_{i<j<k}^{n} \Pr(A_i \cap A_j \cap A_k) - \ldots
\]

In the NSAID assessment we have considered that A1,A2,..., An ailments are independent, therefore we accept:

\[
\Pr(A_i \cap A_j) = \Pr(A_i) \times \Pr(A_j), i \neq j,
\]

\[
\Pr(A_i \cap A_j \cap A_k) = \Pr(A_i) \times \Pr(A_j) \times \Pr(A_k), i \neq j \neq k
\]

Below we have estimated \( F(NSAIDs) \) by calculating the probability of not getting either of the A1,A2,..., An ailments, namely

\[
\Pr(\text{non}(A_1 \cup A_2 \cup \ldots \cup A_n)) = \Pr(\text{non}(A_1) \cap \ldots \cap \text{non}(A_n))
\]

However, based on independence of criteria the following result:

\[
\Pr(\text{non}(A_1 \cup A_2 \cup \ldots \cup A_n)) = \Pr(\text{non}(A_1)) \times \ldots \times \Pr(\text{non}(A_n)) = (1 - \Pr(A_1)) \times \ldots \times (1 - \Pr(A_n))
\]

Therefore NSAID assessment can be made according to the following formula:

\[
F(AINS) = 1 - (1 - \Pr(A_1)) \times \ldots \times (1 - \Pr(A_n))
\]

The Global Risk Method includes the following steps:

Step 1. Risk probabilities are calculated \( r_{is} = 1,2,\ldots,14; j = 1,2,\ldots,13 \)

Step 2. Weighted risk probabilities are determined by weights scale by using the formula:
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Step 3. The global risk is estimated for each NSAID by

\[ F(A_{iNS}) = 1 - \prod_{j=1}^{n} (1 - v_{ij}) \]

Step 4. NSAIDs are ranged increasingly according to their global risks.

\[ F(A_{iNS}) = 1 - \prod_{j=1}^{n} (1 - v_{ij}) \]

**Maximum Risk Method (MRM)**

In this approach we have considered the following risk criteria: cutaneous SE, gastrointestinal SE, hepatic SE, renal SE, cardiovascular SE, nervous SE, musculoskeletal SE, severe cardiovascular risk and Inefficiency and R SE.

I am going to assess each NSAID by estimating the maximum risk probability for any of \( A_1, A_2, ..., A_n \) side reactions. By MRM, NSAIDs are ranked in increasing order according to the maximum risk.

The **Maximum Risk Method** includes the following steps:

Step 1. Risk probabilities are calculated based on data \( r_{ij}, s = 1, 2, ..., 14; j = 1, 2, ..., 13 \)

Step 2. Criteria weights are situated on a scale according to the formula:

\[ w'_j = \min\{w_{k,j}, k = 1, 2, ..., 13\} \]

Step 3. Risk probabilities are weighted by weights situated in step 2 scale

\[ v'_{ij} = r_{ij} w'_j, s = 1, 2, ..., 14; j = 1, 2, ..., 13 \]

Step 4. The maximum risk is estimated for each NSAID by

\[ F(A_{iNS}) = \max\{v'_{ij} | j = 1, 2, ..., 13\} \]

Step 5. NSAIDs are ranged increasingly according to maximum risks, the best being the one with the lowest maximum risk.

**Results**

Results obtained by **Global Risk Method**

The resulting ranking in the global risk approach is presented in Table 1, where the global risk for each NSAID is determined by the formula (3).

<table>
<thead>
<tr>
<th>No</th>
<th>NSAID</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nimesulide</td>
<td>0.227092</td>
</tr>
<tr>
<td>2</td>
<td>Etoricoxib</td>
<td>0.392118</td>
</tr>
<tr>
<td>3</td>
<td>Celecoxib</td>
<td>0.430254</td>
</tr>
<tr>
<td>4</td>
<td>Acetaminofen</td>
<td>0.489999</td>
</tr>
<tr>
<td>5</td>
<td>Naproxen</td>
<td>0.504021</td>
</tr>
<tr>
<td>6</td>
<td>Tenoxicam</td>
<td>0.533404</td>
</tr>
<tr>
<td>7</td>
<td>Ibuprofen</td>
<td>0.546035</td>
</tr>
<tr>
<td>8</td>
<td>Meloxicam</td>
<td>0.553035</td>
</tr>
<tr>
<td>9</td>
<td>Piroxicam</td>
<td>0.568072</td>
</tr>
<tr>
<td>10</td>
<td>Ketorolac</td>
<td>0.589887</td>
</tr>
<tr>
<td>11</td>
<td>Diclofenac</td>
<td>0.633493</td>
</tr>
<tr>
<td>12</td>
<td>Ketoprofen</td>
<td>0.642766</td>
</tr>
<tr>
<td>13</td>
<td>Etodolac</td>
<td>0.661972</td>
</tr>
<tr>
<td>14</td>
<td>Indometacin</td>
<td>0.759393</td>
</tr>
</tbody>
</table>

The minimum global risk anti-inflammatory is Nimesulide, closely followed by Etoricoxib and
Celecoxib.

Results Obtained by the Maximum Risk Method

Determining and ranking by order of growth the maximum risk for each NSAID, where the maximum risk is calculated based on formula (5) the following new ranking results in non-steroidal anti-inflammatory drugs:

<table>
<thead>
<tr>
<th>No</th>
<th>NSAID</th>
<th>RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nimesulide</td>
<td>0.1883</td>
</tr>
<tr>
<td>2</td>
<td>Etoricoxib</td>
<td>0.3004</td>
</tr>
<tr>
<td>3</td>
<td>Celecoxib</td>
<td>0.3438</td>
</tr>
<tr>
<td>4</td>
<td>Ibuprofen</td>
<td>0.3642</td>
</tr>
<tr>
<td>5</td>
<td>Acetaminoafen</td>
<td>0.3652</td>
</tr>
<tr>
<td>6</td>
<td>Piroxicam</td>
<td>0.3902</td>
</tr>
<tr>
<td>7</td>
<td>Naproxen</td>
<td>0.3942</td>
</tr>
<tr>
<td>8</td>
<td>Tenoxicam</td>
<td>0.4345</td>
</tr>
<tr>
<td>9</td>
<td>Ibuprofen</td>
<td>0.4859</td>
</tr>
<tr>
<td>10</td>
<td>Acetaminoafen</td>
<td>0.4931</td>
</tr>
<tr>
<td>11</td>
<td>Ketoprofen</td>
<td>0.4954</td>
</tr>
<tr>
<td>12</td>
<td>Meloxicam</td>
<td>0.4995</td>
</tr>
<tr>
<td>13</td>
<td>Indomethacin</td>
<td>0.5029</td>
</tr>
<tr>
<td>14</td>
<td>Etodolac</td>
<td>0.5792</td>
</tr>
</tbody>
</table>

The lowest found minimum risk anti-inflammatory is Nimesulide, closely followed by Etoricoxib and Celecoxib as with the GRM, and the last in the ranking are Etodolac and Indomethacin (in reversed order as compared to GRM)

<table>
<thead>
<tr>
<th>MRG</th>
<th>Correlation Coefficient</th>
<th>p</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRGX</td>
<td>1.000</td>
<td>0.0000025</td>
<td>14</td>
</tr>
<tr>
<td>MRMX</td>
<td>.897**</td>
<td>1.000</td>
<td>14</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed).
N - number of alternatives

When comparing GRM and MRM rankings we find a significantly high Spearman correlation (p > 0.897), the two approaches yielding similar rankings, even if the results are different.

Discussion

Pain management represents one of the situations often met by clinicians. The challenge is to find the most efficient treatment, which is the closest to the general clinical information sheet of a patient and generate the least side effects. Used for the management of many symptoms and pathologies, non-steroidal anti-inflammatory drugs continue to be among the widest prescription drug classes in the whole world, being recommended in decreasing pain and the anti-inflammatory process. It is considered that over 30 million people are daily on NSAID medication and about half of them are elderly people [66]. Approximately 25% of the total side effects generated by the
consumption of drugs are caused by NSAIDs, over one hundred thousand hospital admissions being recorded and over 16000 annual deaths caused exclusively by gastrointestinal side effects of NSAIDs [4, 67].

Result accuracy in the ranking issue can be influenced by criteria-related errors, the chosen ranking criterion, as well as by the transcription of initial data and even the number of criteria and alternatives. The ranking process should not include irrelevant criteria or omit relevant ones, as this may also lead to wrong results.

Criteria weight rates represent a subjective factor within the ranking techniques, which may influence the order of alternatives, from one decision maker to another. The relative importance of criteria differ according to the significance awarded by each decision administrator for each and every criterion, meaning that different decision makers may award different degrees of importance to criteria, differently underlining their importance, and this may generate totally different results and, implicitly, conflicts between the rankings of different decision makers.

For example, the weights we have attributed to criteria within the NSAID ranking can be considered non-accurate and disputed by another clinician.

We have considered that treatment failure (due to inefficiency) and abandon (following annoying side effects in a patient) weigh the most in establishing the NSAID ranking, whereas cutaneous and musculoskeletal side effects have been attributed minimum weights by us. For side effects, we have also attributed a high weight to severe cardiovascular events occurred during the NSAID treatment, closely followed by gastrointestinal side effects. Another decision maker might have awarded lower weight to gastrointestinal effects having an increased incidence, and being associated to a large number of hospitalizations.

If probability represents the occurrence probability of an event, the risk represents the chance to produce an unwished event as well as the seriousness of consequences generated by the event. Assessing or estimating the risk resides in risk prioritization.

In order to achieve a NSAID ranking by GRM, we have assessed each of the fourteen non-steroidal anti-inflammatory drugs and estimated the probability of global risk for one of the considered side effects.

The method principle consists of quantifying the risk as the product between risk weight and risk probability, and the safety level will be in reverse proportion to its level. After estimating the global risk for each NSAID, it was easy to range the NSAIDs according to the increasing levels of their global risks, safety profiles of Nimesulide, Etoricoxib and Celecoxib proving superior to the other NSAIDs, whereas Ketoprofen, Etodolac and Indomethacin are more likely to risk side effects.

Non-steroidal anti-inflammatory drugs represent a largely prescribed class of drugs in the symptomatic treatment of pain and inflammation, which is why we should not forget that a part of their side effects are more important and more severe than the ailment for which they have been initially administered. By the Maximum Risk Method we have established a NSAID ranking based on the maximum risk represented by each non-steroidal anti-inflammatory drug for each type of side effect.

On the top of the two rankings there are Nimesulide, Etoricoxib and Celecoxib, Nimesulide confirming a safety profile better than the rest of NSAIDs. Literature data seem to support it as well, therefore resulting that Nimesulide possesses a weak potential for gastrointestinal complications and cardiovascular [23-26,37,41,68,69]. Taking into account all the spontaneous reports of gastrointestinal side effects, Nimesulide has been associated to only half of the number reported for other NSAIDs (Diclofenac, Ketoprofen, Piroxicam)[4]. Compared to Naproxen, its action upon platelet aggregation is insignificant (does not produce bleeding by favoring pro-aggregation TXB2 production and does not generate thromboembolic complications by favoring pro-aggregation PGI2 production) [69].

The fact that we cannot completely eliminate side effects of a treatment, and therapeutic alternatives present more other risks, makes their correct prioritizing an important measure in the medical decision.

As for Etoricoxib, ranking two on minimum risk level, regardless of the method used, five of the seven studies from which we have extracted data upon which the NSAID ranking has been
made, have been either sponsored, or the authors were collaborators of Etoricoxib producer, this aspect making results objectivity a bit doubtful.

Conclusions

Considering the risk of each NSAID, by two separate ranking methods we have determined Nimesulide, Etoricoxib and Celecoxib to have a safety profile superior to the other NSAIDs, whereas Etodolac and Indomethacin present an increased side effects risk.

Beside the fact that they are not large information and time consumers, the Global Risk Method and the Maximum Risk Method can be a useful instrument in therapeutic alternative (NSAID) with the lowest risks.

The results of this study confirm the fact that ranking method approach in the medical field can offer clear advantages in therapeutic decisions.

List of abbreviations (if any)

- NSAID Non-steroidal anti-inflammatory drug
- GRM Global Risk Method
- MRM Maximum Risk Method
- SE Side effects

Conflict of Interest

The authors declare that they have no conflict of interest.

References

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