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Non-Steroidal Anti-Inflammatory Drugs Ranking by Nondeterministic Assessments of Interval Data Type

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Abstract
Since there are no major differences in terms of their efficiency, the choice of an NSAID regimen is naturally to be directed towards those NSAIDs that have proven a favourable safety profile (low side effects). However, it should be remembered that the risk of side effects may change depending on dose and time of administration. Considering the properties of an "ideal" NSAIDs (high efficiency, low toxicity - minimal side effects, simple regimen, reduced abandon rates, increased treatment compliance, reduced cost), we determined the hierarchy of fourteen NSAIDs through two statistical methods adjusted to the interval data, ITPOSIS1 and ITPOSIS2. The different hierarchies obtained by the two methods are justified by the difference between the two ranking methods, namely the method to calculate the distance to the ideal solution.

Keywords: NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) ranking; NSAIDs side effects (SE); Ranking methods; Interval technique for order preference by similarity to ideal Solution.

Introduction

The non-steroidal anti-inflammatory drugs (or NSAIDs) are a class of medicines used to reduce pain, stiffness, and inflammation. There are two main types of NSAIDs: nonselective NSAIDs and COX-2 selective non-steroidal anti-inflammatory, each with their advantages and disadvantages.

The anti-inflammatory, analgesic and antipyretic action, and their efficacy and toxicity are closely related to plasma concentration, half-life, peak plasma clearance, and with cyclooxygenase (COX)-1 and COX-2 inhibition [1].

The main objective of this study was to determine the ranking of fourteen non-steroidal anti-inflammatory drugs considering: the risk of side effects occurrence, their efficiency (half-time and peak time), or the treatment failure or abandon rates or low compliance with the treatment (number of administrations per day, the price of treatment per day).

Material and Method

In order to gather all the relevant information, we have used original articles and meta-analyses study types selected using the PubMed 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. We have selected those studies containing relevant information related to the number of patients included in the studies and the number of side effects generated by the administration of a NSAID [2-49]. We consulted, in parallel, the websites of pharmaceutical regulatory authorities.

The properties of an ideal NSAID (high efficacy, low toxicity, easy administration, low abandon rate and low cost) are defined by a set of criteria that can influence NSAIDs ranking:

- the half -life (is the time in plasma concentration of a substance is halved and may vary from one anti-inflammatory drug to another);
- time to reach peak plasma concentration (indicates the expected time for the therapeutic effect; gives clues on the absorption rate, resulting in the time in which the maximum plasma concentration is reached both in plasma and at specific receptor level);
- cost of treatment per day;
- efficiency and compliance to treatment is influenced by the number of doses per day;
- side effects: cutaneous SE, gastrointestinal SE, hepatic SE, respiratory SE, renal SE, urinary SE, cardiovascular SE, nervous SE, musculoskeletal SE, severe cardiovascular risk (cardiovascular death, myocardial infarction, stroke);
- abandoning the treatment due to side effects uncomfortable for the patient;
- treatment failure (inefficiency).

Because the nineteen criteria considered in NSAIDs prioritizing, not having the same units, we transformed the data collected in interval data. We used the TOPSIS method, proposing two variants ITPOSIS1 and ITPOSIS2, tailored to the interval data assessments. The criteria were assessed separately, independently one from each other.

The complexity of ranking increases when there are more variants dependent on a large number of conflicting criteria. Consequently, there will be an increase in the number and nature of the uncertainty factors. NSAIDs assessment matrix included a score type criteria, fourteen risk criteria (cutaneous SE, gastrointestinal SE, hepatic SE, respiratory SE, renal SE, urinary SE, cardiovascular SE, nervous SE, musculoskeletal SE, severe cardiovascular risk (cardiovascular death, myocardial infarction, stroke), two criteria in the data interval form ($T_{1/2}$, T peak) that measure the time, and two determinist criteria (price and number of doses per day). The aim was to order alternatives (NSAIDs) from the most efficient to the least efficient in relation to all criteria.

The ITOPSIS Method to Rank the Interval Based Criteria

The TOPSIS method determines which alternative is the closest to the ideal solution. The alternative with the shortest distance from the positive ideal solution and the farthest distance from negative ideal solution is considered the most powerful. The ranking of the alternatives is based on the comparison of their distance to the positive and the negative ideal solution. An advantage of this method is that it can be used with both quantitative and qualitative data; thus TOPSIS method is a flexible method.

In this study, a different approach of TOPSIS method has been developed to rank the interval based criteria. ITOPSIS method for interval data evaluation is based on [50,51]:

- the evaluation matrix $C = (c_{ij})$
- the vector $W = (w_1, ..., wn)$ of weights of the criteria.
- calculating a vector - the ideal solution vector, which includes best values for each criterion, the optimal alternative should be as close as possible to the ideal solution

Hereinafter, for the intervals [a,b], [c,d], $a \leq b$, $c \leq d$ by definition, it is considered:

$$\max\{[a,b],[c,d]\} = [\max\{a,c\}, \max\{b,d\}]$$

$$\min\{[a,b],[c,d]\} = [\min\{a,c\}, \min\{b,d\}]$$

The Ranking Algorithm for ITOPSIS1

The ITOPSIS1 algorithm consists of the following steps:

Step 1. The normalized matrix is determined using $\Omega = r_{ij}$

Step 2. The weighted normalized matrix is determined $V = v_{ij}$, where $v_{ij} = w_j r_{ij}$

$v_{ij} = [v'_{ij}, v''_{ij}]$, i=1,2,...,m; j=1,2,...,n, where $v'_{ij} = w_j r'_{ij}, v''_{ij} = w_j r''_{ij}$ whatever i=1,2,...,m; j=1,2,...,n.

Step 3. The positive ideal solution is determined $v^* = ([\bar{v}_1, \bar{\bar{v}}_1],..., [\bar{v}_n, \bar{\bar{v}}_n]$ (i.e. the vector of the best range of values of the alternatives for criteria) and the negative ideal solution $v^- = ([\underline{v}_1, \underline{\underline{v}}_1],..., [\underline{v}_n, \underline{\underline{v}}_n])$ (i.e. the vector of the weakest range of values of the alternatives for criteria), where

$$\bar{v}_j = \begin{cases} \max\{v'_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \max \\ \min\{v'_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \min \end{cases}$$

$$\bar{\bar{v}}_j = \begin{cases} \max\{v''_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \max \\ \min\{v''_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \min \end{cases}$$

$$\underline{v}_j = \begin{cases} \min\{v'_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \max \\ \max\{v'_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \min \end{cases}$$

$$\underline{\underline{v}}_j = \begin{cases} \min\{v''_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \max \\ \max\{v''_{ij} \mid 1 \le i \le m\}, \text{ pentru } T(K_j) = \min \end{cases}$$

Step 4. It is calculated for each alternative the "distance" from the two ideal solutions

$$d_i^* = \sum_{j=1}^{n} \left(| v'_{ij} - \bar{v}_j | + | v''_{ij} - \bar{\bar{v}}_j | \right),$$

$$d_i^- = \sum_{j=1}^{n} \left(| v'_{ij} - \underline{v}_j | + | v''_{ij} - \underline{\underline{v}}_j | \right), \text{ i=1,2,...,m}$$

Step 5. It is determined for each alternative, the relative closeness coefficient to the ideal solution

$$\delta_i = \frac{d_i}{d_i^* + d_i}, \text{ i=1,2,...,m;}$$

One can easily see that there is always $0 \le \delta_i \le 1$, i=1,2,...,m;

An alternative A_i is closest to the ideal solution if the relative closeness coefficient approaches to 1.

Step 6. Ideal alternative and a ranking of all alternatives can be made according to the closeness coefficients in descending order δ_i (i = 1,2, …, m).

The ITOPSIS1 method for ranking the interval based criteria extends the classical TOPSIS method presented, for example, in the works [50,51].

The Ranking Algorithm for ITOPSIS2

Compared to ITOPSIS1 method, the ITOPSIS2 method may include a change in the indicator calculation of the Step 4, as they are influenced by the long intervals of ranking, as follows:

$$d_i^* = \sum_{j=1}^{n} (| v'_{ij} - \bar{v}_j | + | v''_{ij} - \bar{\bar{v}}_j |)(v''_{ij} - v'_{ij} + 1),$$

$$d_i^- = \sum_{j=1}^{n} (| v'_{ij} - \underline{v}_j | + | v''_{ij} - \underline{\underline{v}}_j |)(v''_{ij} - v'_{ij} + 1), \; i=1,2,...,m.$$

The other steps of the algorithm ITOPSIS2 coincide with those of the ITOPSIS1 method.

Results

By using the NSAIDs ranking and applying the normalization methods, normalized matrix was determined, and then it was turning into normalized weighted matrix. The positive and negative ideal solution was calculated, according to which, the "distance" from the two ideal solutions and the relative closeness coefficient to the positive ideal solution was calculated for each alternative, finally ranking in descending order the fourteen non-steroidal NSAIDs according to the relative closeness coefficient values.

The two NSAIDs rankings obtained after the application of the ITOPSIS1 method (T1) and ITOPSIS2 method (T2) are presented in the Table 1.

Table 1. NSAIDs ranking related to risk criteria, efficiency, cost, compliance:

T1	Ranking	T2
Etoricoxib	1	Etoricoxib
Nimesulide	2	Nimesulide
Piroxicam	3	Ibuprofen
Celecoxib	4	Celecoxib
Ketorolac	5	Piroxicam
Tenoxicam	6	Acetaminoafen
Acetaminoafen	7	Tenoxicam
Ibuprofen	8	Naproxen
Ketoprofen	9	Ketorolac
Naproxen	10	Meloxicam
Meloxicam	11	Ketoprofen
Etodolac	12	Etodolac
Diclofenac	13	Diclofenac
Indometacin	14	Indometacin

T1 = ranking NSAIDs by ITPOSIS1;
T2 = NSAIDs ranking by ITPOSIS2;
1,2,3…14 = the position in the ranking

Etoricoxib, Nimesulide, Ibuprofen, piroxicam and celecoxib are the most effective and safe NSAID, with a good cost / efficiency / compliance ratio, as long as the SPC indications overlap the patient's diagnosis. Indomethacin, Diclofenac and Etodolac are far from "ideal" NSAIDs image.

As shown in Figure 1, the T1 and T2 ranking, obtained by ranking methods, i.e. ITOPSIS1 and ITOPSIS2, are different; however, they have the same first two elements (Etoricoxib and Nimesulide). Also, there are four non-steroidal NSAIDs with a similar position in the ranking; the two rankings have the same upward trend.

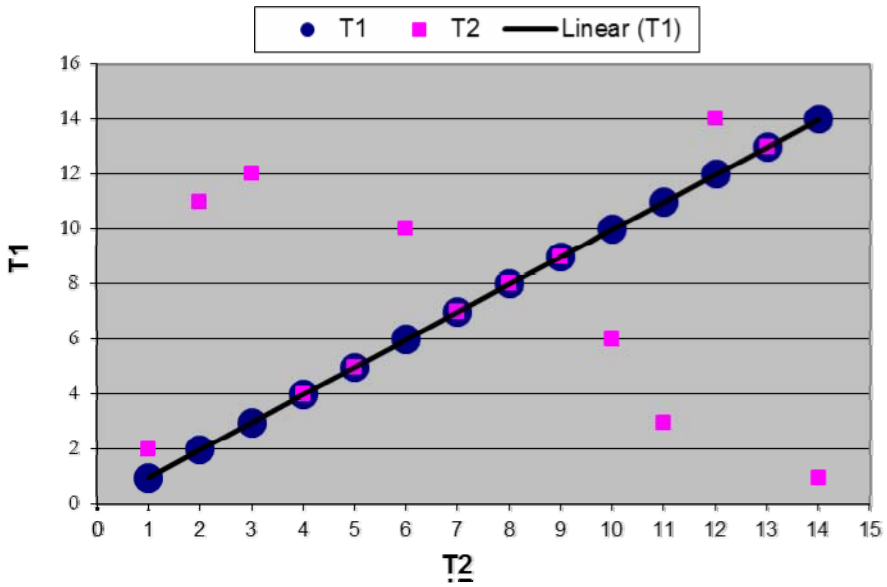

Figure 1. The dispersion of the T1 ranking related to T2 ranking

According to this result, the ITOPSIS2 method gives significantly different results compared to ITOPSIS1, although the first two and the last three positions are occupied by the same NSAIDs. The differences between the two rankings are justified by the different ways of calculating of the distance to the ideal solution.

Discussion

Thorough knowledge of each NSAID side effects and risks can be useful for minimizing the adverse reactions in the patients risk groups and supporting appropriate use of medicines. Since no one can accurately predict the likelihood of a patient to experience side effects as a result of the NSAID use, we considered as an information interval. The different method to calculate the distance to the ideal solution (step number four in the calculation algorithm of the method TOPSIS) explains different ordering for each method. The difference between the two rankings, should not be cause for concern; more important than the similarity of the entire ranking is that of the alternatives found at the top and the lowest level of the hierarchy.

Result accuracy in ranking issues may be influenced by errors regarding the criteria and the chosen ranking technique, as well as by initial data transformation or the number of criteria and alternatives. The ranking process must not include irrelevant criteria. Neither must it omit relevant criteria, as both may lead to erroneous results.

The weight assigned to criteria represents a subjective factor within ranking techniques, which may influence the order of alternatives from one decision maker to another. The relative importance of criteria varies according to the weight assigned to each criterion by each decision maker in particular. This means that different decision makers may place different emphasis on different criteria, thereby generating completely different results and conflicts between the rankings.

For instance, the weight assigned to the criteria in the course of NSAID ranking (10 for $T_{1/2}$, 10 for T peak, 15 for COX-2/COX-1 criteria, 15 for price of treatment/day, 15 for no. of doses/day, 8 for cutaneous SE , 30 for gastrointestinal SE, 25 for hepatic SE , 12 for respiratory SE, 19 for renal SE, 16 for urinary SE, 30 for cardiovascular SE, 20 for nervous SE, 9 for musculoskeletal SE, 80 for cardiovascular death, 50 for myocardial infarction, 60 for stroke, 85 for abandoning the treatment due to side effects uncomfortable for the patient and 90 for treatment failure) may be considered as lacking accuracy and it may be contested by another clinician. We have considered treatment failure (due to inefficacy) and abandonment (as a result of unpleasant adverse effects) as

major factors when ranking NSAIDs, whereas cutaneous and muscular side effects appear to be minor factors. With regard to adverse effects, among high risk factors of an NSAID-based treatment are cardiovascular events, followed closely by gastrointestinal reactions. Another decision maker may have placed greater emphasis on the latter since GI reactions have been associated with a great number of hospitalizations.

NSAIDs, although belonging to the same pharmacological class with many similarities, yet each of them have certain particularities that are reflected in specific side effects. Thus, if the inhibition of COX-1 by traditional NSAIDs accounts gastrointestinal and renal side effects, and the inhibition of COX-2 by traditional NSAIDs accounts for cardiovascular side effects, there are also NSAIDs individual peculiarities. For example: indomethacin was found to give many serious side effects to the CNS [26], nimesulide has been attributed a high percentage of side effects in the liver [52], ibuprofen at doses that exceed 2400 mg may cause an increased risk of serious cardiovascular events [53], etoricoxib despite being a COX-2 inhibitor, EMA warned about its high risk of serious gastrointestinal toxicity, and as regards the use of celecoxib, FDA (April 2005) and EMEA (June 2005) imposed restrictions on use in patients with cardiovascular disease which can influence the development of thrombotic events [54] and the examples could continue.

Returning to the two rankings of AINS, ITOPSIS1 and ITOPSIS 2, we notice that the first two positions, and the last three positions are identical; Etoricoxib, Nimesulide and Celecoxib are the best options, while Etodolac, Indomethacin and Diclofeanc would be the least inspired choices.

Analysing the specialized literature in the field [2-6,15-17,48], these recommendations appear to be justified since the gastric, renal and cardiovascular incidence were shown to be lower for coxibes than in the traditional NSAIDs.

There is still a debate to estimate the extent to which a combination of a traditional NSAID with a proton pump inhibitor is associated with low gastrointestinal risk compared with coxibes [55-67]. Although COX-2 selective NSAIDs are considered to have minimal risk for gastric complications, it should not be overlooked. EMA took notice of the gastrointestinal risks presented by etoricoxib, especially in patients treated with salicylsalicylic acid or in patients receiving high doses for extended periods of time [57,61-63]. EMA warned of the gastrointestinal risk presented by several NSAIDs (meloxicam, piroxicam).

Rodriguez (2001), made a NSAID uni-criteria ranking according to gastrotoxicity, where indomethacin and diclofenac occupy the lowest positions, overcame by piroxicam, and the first positions occupied by etodolac and ibuprofen [53]. Minea et al. [65] made a uni-criteria ranking of eight non - steroidal NSAIDs depending on the gastrointestinal side effects associated with NSAID (patients hospitalized as a result of these drugs administration); nimesulide and etoricoxib are among the top positions, with the lowest percentage of gastrointestinal adverse reactions, followed by Indomethacin, Diclofenac, Piroxicam, Ketoprofen, Meloxicam, Celecoxib and Ibuprofen in the last position. Other authors also determined the uni-criteria ranking of NSAIDs based on their gastrotoxic effects, but without taking into account factors such as efficiency, cost, compliance and the way these can affect any organ or system, including the cardiovascular, renal, nervous systems, etc., (the two hierarchies do not neglect these aspects). From this point of view, the ITPOSIS1 and ITOPSIS2 ranking methods provide a wider perspective of NSAIDs, taking into account criteria that until now have not been considered.

Even though it occupies a top position among NSAIDs, etoricoxib presents increased incidence of thrombotic events (class effect), depending on dosage [4]. In 2008, after a period of Etoricoxib cardiovascular risk assessment, the EMA and FDA warned on this issue compared with other NSAIDs (increases three times the risk of heart attack, stroke and death compared to naproxen) [54]. Unlike Etoricoxib, Ibuprofen and Celecoxib, Nimesulide demonstrated a cardiovascular safety profile superior to other NSAIDs [68].

The non-selective NSAIDs have a relatively high potential for cardiovascular incidence [67]. There are studies that have shown that even in the short-term use of NSAIDs for acute diseases, the cardiovascular risk is increased both in patients with pre-existing cardiovascular disease and in patients with low risk profile [68,69], diclofenac shows the highest cardiovascular risk, while ibuprofen and naproxen the lowest [68]. Indomethacin, besides its high cardiovascular risk, is associated with a high percentage of adverse gastrointestinal effects and central nervous system-

related effects, which making questionable recommendation on future therapeutical schemes.

Indomethacin, piroxicam and ibuprofen were frequently accused for renal disorders; the risk of renal impairment is variable depending on the dosage, and the risks increase with higher doses [70-72]. Clinical and experimental studies have shown that both non selective NSAIDs and the selective COX-2 inhibitors have the same risk for kidney complications, resulting in urine sodium decreased, oedema and increased blood pressure [70,72].

Scheiman [73] and NICE [74], considering the traditional NSAIDs and the coxibes of similar efficiency, only varying the degrees of gastrointestinal, cardiovascular, and kidney toxicity, (depending on dosage, concentration and duration of treatment) recommend that while choosing an anti-inflammatory treatment, the risk factors in patient should be considered together with the therapeutic guidelines and the NSAIDs prescriptions in SPC.

As noted, the specialised literature does not provide consistent data on the risk and effectiveness of NSAIDs. The rankings in the studies, generally, take into account a limited number of NSAIDs, determined based on a single criteria (the risk of gastric and cardiovascular problems being targeted more frequently) and only few of them have taken into account the cost / efficiency ratio. Besides, there are several drug regulatory agency warnings (FDA, EMA) for almost each NSAID. All this can create stressful situations for the doctor. Through the two ITPOSIS ranking methods, we offered an objective basis for medical decision, providing thorough assessments and comparative information on therapeutic alternatives based on the performance criteria chosen by the therapist.

Weaknesses of the Study

As regards Etoricoxib, placed on the first position in the ranking, regardless of the method used, five of the seven studies [2,15,47-49] from which we extracted the data, were either sponsored or the authors were collaborators with the company manufacturing the Etoricoxib, so this questioning the objectivity of the results.

As regards Etodolac, the last position in the ranking, the data was provided only by two studies, without sufficient data for all types of risk, and their volume does not accurately render clinical reality.

Conclusions

Etoricoxib, Nimesulide, Piroxicam, Ibuprofen and Celecoxib are the clinicians rational choice among patients who take NSAIDs, as being the most effective and safe NSAID, with a good cost / efficiency / compliance ratio, as long as the RCP indications overlap the patient's diagnosis. Indomethacin, Diclofenac and Etodolac are far from "ideal" NSAIDs image.

The results of this study confirm that the ranking approach in the medical field can offer clear advantages in therapeutic decisions and can assist physicians in choosing an appropriate NSAID treatment strategy.

List of abbreviations

NSAID: Non-steroidal anti-inflammatory drug
EMA: European Medicines Agency
FDA: Food and Drug Administration
SE: Side effects
TOPSIS: Technique for Order Preference by Similarity to Ideal Solution
ITOPSIS: Interval Technique for Order Preference by Similarity to Ideal Solution
SPC:Summary of Product Characteristics

Conflict of Interest

The authors declare that they have no conflict of interest.

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