The Challenge of Assessing Benefit-Risk of Older Drugs

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Evidence-based pain therapy should rely on precisely defined and personalized criteria. This includes balancing the benefits and risks not only of single drugs but often requires complex between-drug comparisons. Non-steroidal anti-inflammatory drugs (NSAIDs) have been available for several decades and their use is described in an abundance of guidelines. Most of these guidelines recommend that 'the selection of a particular NSAID should be based on the benefit-risk balance for each patient'. However, head-to-head studies are often lacking or of poor quality, reflecting the lower standards for clinical research and regulatory approval at the time. The inconsistency of approved indications between countries due to national applications adds to the complexity. Finally, a fading research interest once drugs become generic points to a general deficit in the post-marketing evaluation of medicines. Far from claiming completeness, this research illustrates the challenges that physicians encounter when trying to balance benefits and risks in a situation of incomplete and inconsistent data on longstanding treatment concepts. Ibuprofen and mefenamic acid, the most frequently sold NSAIDs in Austria, serve as examples. The illustrated principles are, however, not specific to these drugs and are generalizable to any comparison of older drugs in daily clinical practice.

Keywords: ibuprofen ; mefenamic acid ; non-steroidal anti-inflammatory drugs ; pain medication

1. Introduction

Pain is not a simple, precisely defined neuronal sensation but rather a complex series of pathophysiological, emotional, and behavioral processes. An Austrian survey among patients suffering from pain reflects this complexity when reporting that around 40 to 65 percent of respondents were dissatisfied with their treatment and frustrated by the care received.[1][2] A comprehensive assessment of an individual's needs and a tailored, multimodal, and interdisciplinary treatment strategy in accordance with international standards are thus warranted.[3][4][5] Especially in the treatment of acute pain, rapid therapy within the limits of the drug's pharmacokinetic properties is important to avoid the occurrence of manifest changes in the central nervous system and thus pain chronification.[6][7] Chronic pain, however, is best treated at a fixed administration schedule allowing for a stable effect throughout the day.[6][7]

Non-steroidal anti-inflammatory drugs (NSAIDs) represent a large class of pain killers, of which most representatives have been available for several decades. However, recent research, especially high-quality head-to-head trials are often lacking, reflecting the lower standards for clinical research and regulatory approval at the time these drugs came to market. This complexity of pain management at all stages underlines the importance of comprehensive and evidence-based consultation at the patients' point of contact, i.e., the doctor's office or the pharmacy.

To reduce complexity while providing up-to-date clinical evidence, well-maintained guidelines are available to physicians and pharmacists.[3][8][9][10] Most guidelines recognize this unsatisfactory situation and shift the responsibility for individual assessment of the benefit-risk balance to the consultant. A typical statement is the following:[10] 'Overall, most evidence showed no significant efficacy differences among the different non-selective NSAIDs. However, the quality of evidence for the majority of indications was limited by small and underpowered studies with imprecise estimates of effect and the absence of several randomized, controlled trials (RCTs) for the same non-selective NSAID comparison. Additionally, RCTs for every possible NSAID comparison are lacking. Guidelines, across indications, do not specify a preference for one non-specific NSAID over another.' Sometimes this is followed by a disclaimer, such as the following:[3] 'Practitioners should choose medication within their appropriate prescribing rights and within their scope of professional practice and accept clinical/legal responsibility for their prescribing decisions.' The present research illustrates the challenges that physicians encounter when trying to balance benefits and risks in a situation of incomplete and inconsistent between-drug comparisons of longstanding treatment concepts. Ibuprofen and mefenamic acid in their locally approved Austrian indications have been chosen as examples. This research is not trying to provide a complete summary of the literature

available to date but rather to illustrate a principle, which is generalizable to any comparison of older drugs in daily clinical practice.

2. Pain Management in the Course of Time

NSAIDs are the largest and most commonly prescribed type of analgesic. Many compounds are available prescription-free through pharmacies or over-the-counter (OTC) for self-medication. As a general consideration it should be noted that all substances that have obtained national or regional regulatory approval were considered effective and safe in their respective indication by the regulatory authorities.[11] In Austria, the NSAIDs acetylsalicylic acid, paracetamol and ibuprofen are OTC drugs, while mefenamic acid requires a prescription.[12] In other countries, however, OTC preparations for mefenamic acid are available. Reference is made to local regulatory agencies for the respective prescribing information.

According to a report by the Austrian Federal Environment Agency,[13] the total consumption of analgesics, anti-inflammatory drugs and anti-rheumatic agents in Austria in 2014 was 244,854 kg. Compared to 1997, this represents an increase of 50%. There was also a shift in the individual compounds most frequently used: while in 1997 acetylsalicylic acid, paracetamol and mefenamic acid were among the three most commonly used compounds in Austria, acetylsalicylic acid was increasingly replaced by ibuprofen by 2014.[13][14] Among NSAIDs, this leaves ibuprofen and mefenamic acid as preferred choices in Austria, often for similar indications. Lacking comprehensive head-to-head trials, the choice of compound is also often guided by individual experience and preference of the physician, the pharmacist and even the patient. Even the comprehensive compendium “Martindale—the Complete Drug Reference” points out that the medical prescription is often based only on doctors’ experience.[15]

3. History of NSAIDs and Its Impact in Data Quality Today

NSAIDs represent one of the oldest classes of medicines. They are typical representatives of the era of chemistry-driven drug research, which was dominant until the middle of the 20th century and was eventually replaced by targeted (pharmacology-driven) drug design. Acetylsalicylic acid is a typical example of chemistry-driven drug design. It was initially developed as a prodrug of salicylic acid, designed with the aim to avoid the adverse effects of its parent compound. It was only much later found to be an irreversible enzyme blocker perfectly suited as antithrombotic drug. Mefenamic acid received its first market approval in 1962 in the United States.[16] Ibuprofen was first approved in the United Kingdom in 1969.[17] At the time of market entry, the basic mechanisms of action were not yet known. The discovery of the role of the arachidonic acid cascade and of the prostaglandins by Bergström, Samuelson, and Vane was rewarded by the Nobel Prize in Medicine in 1982. Prostaglandin synthase, more frequently referred to as cyclooxygenase (COX), is responsible for the transformation of arachidonic acid to the prostaglandins, prostacyclin and thromboxane. It occurs in two isoforms: COX-1 and COX-2,[18] which were only discovered in 1971 [19] and 1990/91,[20][21] respectively. In the meantime, extensive pharmacological work on the arachidonic acid cascade has revealed the high complexity of this system, which increasingly will be recognized to be the core of innate immunity.

This iterative procedure stands in considerable contrast to the common drug discovery process today, where a comprehensive package of data on a drug is generated and submitted to inform the regulatory approval process. Marketing approval follows a systematic assessment of all available information on a drug. However, regulatory requirements have evolved in parallel with the scientific progress and also as a consequence of dramatic failures, such as the discovery of the malformations caused by thalidomide in the 1950s and 1960s.[22] Even now, marketing approval is often granted on a preliminary basis with further requests for post-authorization safety studies (PASS), because rare side effects, interactions or risks that only affect certain patient groups only become apparent when a large number of individuals have received the new drug. Available data on old drugs are therefore often incomplete and of low quality as per current standards. Furthermore, with each new chemical entity (NCE) introduced to the market becoming a generic drug after some time (10 to 15 years), the majority of medicines in use consists of products, which have never been subject to a systematic comparative post-marketing assessment guided by drug authorities according to current standards.

4. Conclusions

It was mentioned before that most of the NSAIDs are very old drugs and that this class of compounds received renewed attention only after the discovery of underlying physiological mechanisms. At that time, mefenamic acid already was a generic drug of limited interest for industry, while ibuprofen became one of those drugs that benefited from the new

mechanistic “boom”. It received a further stimulus by the upcoming “racemic drug” topic, which led to the discovery of dexibuprofen.

Comparative data of both compounds are rare. A benefit–risk assessment based solely on the degree of COX-1 or COX-2 selectivity is not permissible. Both drugs are currently approved, therefore they can be considered effective and safe in the approved dose and in the short-term setting. It is known that a ceiling effect at higher doses occurs with both drugs and no further increase in efficacy can be achieved while toxicity increases in a dose-dependent manner.

For ibuprofen there is recent literature which shows that the cardiovascular and gastrointestinal risk is low at a dosage of up to 1200 mg. In patients with a high cardiovascular risk, however, naproxen should definitely be preferred. Due to the high gastrointestinal side effect profile of naproxen, accompanying gastroprotective medication (e.g., proton pump inhibitors) must be considered. Especially in elderly patients, attention should be paid to existing risk factors and interactions with other frequently administered drugs. In the first two trimesters of pregnancy and during lactation, the safety for ibuprofen is relatively well-established and supported by recent research; for mefenamic acid, however, hardly any recent literature is available. In the third trimester, both drugs are contraindicated. Although both ibuprofen and mefenamic acid—as with the class of traditional NSAIDs in general—have been available for a very long time, conducting further comparative research to better understand the relative efficacy and tolerability of individual NSAIDs should not be neglected. Given the great importance of NSAIDs, the benefit–risk assessment should not be placed on the shoulders of the individual doctors and their individual experience and personal preference alone.

Bearing in mind that post-marketing observation of drug performance has become an indispensable element of surveillance by authorities, it may be considered a major gap in drug utilization that there is no stringent tool for the unbiased direct comparison of (sets of) drugs, not even for the most frequently used of them. Probably only a regulatory initiative could lead to an improved situation.

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