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K Malleswari
Associate professor, Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

D Rama Brahma Reddy
Nalanda Institute of Pharmaceutical Science, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

K Charitha Sri
Nalanda Institute of Pharmaceutical Science, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

D Baji Vali
Nalanda Institute of Pharmaceutical Science, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

G Suresh
Nalanda Institute of Pharmaceutical Science, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

Corresponding Author:
K Malleswari
Associate professor, Nalanda Institute of Pharmaceutical Sciences, Kantepudi, Sattenapalli, Guntur, Andhra Pradesh, India

Non-steroidal anti-inflammatory drugs current challenges and future perceptions

K Malleswari, D Rama Brahma Reddy, K Charitha Sri, D Baji Vali and G Suresh

Abstract
An analytical methodology for the simultaneous determination of seven pharmaceuticals and two metabolites belonging to the non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics therapeutic groups was developed based on off-line solid-phase extraction and ultra-high performance liquid chromatography coupled to tandem mass spectrometry [1] (SPE–UHPLC–MS/MS). Extraction conditions were optimized taking into account parameters like sorbent material, sample volume and sample [1, 2] PH. Method detection limits (MDLs) ranging from 0.02 to 8.18 ng/L were obtained [2, 3]. This methodology was successfully applied to the determination of the selected pharmaceuticals in seawater samples of Atlantic Ocean in the Northern Portuguese coast. All the pharmaceuticals have been detected in the seawater samples, with pharmaceuticals like ibuprofen, acetaminophen, ketoprofen and the metabolite hydroxy ibuprofen being the most frequently detected at concentrations that can reach some hundreds of ng/L [4].

Keywords: Non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase inhibitors, prostaglandins, aspirin

Introduction
Non-steroidal anti-inflammatory are members at a member of drug class that reduces pain, decreases fever, prevent blood clots, and in higher doses decreases inflammation. Side effects depend on the specific drug but lately include an increased risk of gastrointestinal ulcers and bleeds, heart attack, and kidney disease [1]. Drugs, even within safe and limited dosage, in different health conditions, may have potential.

History
In the history of treatment of fever, pain and inflammation is a fascinating tale of human adventure that goes back centuries. Since the discovery and isolation of the salicin from the Willow bark in the early 18th century to the development of the selective cox-2 inhibitor in 1990s, small molecule therapies to treat fever, pain and inflammation has evolved [2, 3]. Traditional NSAIDs such as aspirin, ibuprofen, and diclofenac that exhibit non selective COX inhibition represents some of the most widely prescribed NSAIDs to relive short term fever, pain, and inflammation [4, 5]. The characterstic feature of traditional non selective COX inhibitors NSAIDs [6, 7] was presence of carboxylic acid (COOH) Functional group.In the early 1990s the second isoform of COX was discovered, providing a novel target to develop anti inflamatory agents with superior safety profiles compared to traditional NSAIDs. Consequently, selective COX 2 inhibitors based on diary hetrocyclic ring template as in celecoxib and refecoxib were developed [7, 8].

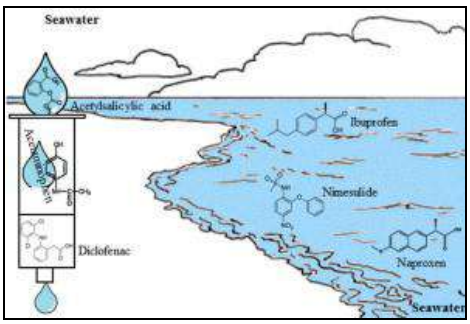

Fig 1: Graphical abstract

Methods

Standards

The systematic review will be performed according to the recommendations specified in the Cochrane Handbook for Interventional Reviews and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

Protocol and registration

We registered our review protocol with the International Prospective Register of Systematic. Ethical approval is not required because this is a literature-based study [6].

Eligibility criteria

Inclusion criteria

Adults' patients with RA diagnosis according to the criteria of ACR or the equivalent criterion in treatment with steroid and NSAIDs at any dose, duration, and route of administration compared to placebo or active control. The type of study included will be randomized controlled trials (RCT) and double blind [7, 8].

Measure outcomes

Primary outcomes

- Decreased pain visual analogy scale in patients with initial pain moderate or severe.
- Improvement of physical function (scales).
- Decreased swelling (VAS and other scales).
- Decreased stiffness (time in minutes or other scales).
- Improvement of grip force (indicator of general strength and general health).
- Progression of the disease through the radiological image of the joints.
- Improvement of quality of life (Short Form-36 and other scales).

Secondary outcomes

- Reports of adverse events including serious adverse events (that cause death, life-threatening, hospitalization, disability, or permanent damage).
- Number of patients reporting any adverse effects.
- Satisfaction with the treatment.
- Consume of rescue medication.

Search methods for primary studies

Electronic searches

We will search the following electronic databases without publication status restrictions: Cochrane Central Register of Controlled Trials, MEDLINE; Excerpta Medica Database; Cumulative Index to Nursing and Allied Health Literature; Web of Science; ClinicalTrial.gov; and WHO International Clinical Trials Registry Platform [1].

Search strategy

The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings and keywords. The search strategy will be designed with the assistance of a trained librarian.

We will use the following MESH terms, with associated keywords: intervention (anti-inflammatory agents); condition (arthritis Rheumatoid), and methodological filters will be applied to limit retrieval to RCT.

Eligibility determination

Six reviewers, working in pairs, will independently monitor potentially relevant citations and abstracts and apply the selection criteria. We will obtain full texts of any article that is considered eligible. The same reviewers will independently evaluate the eligibility of each full-text article.

Data extraction

The same reviewers, working in pairs, will independently extract the data and will record information regarding patients, methods, interventions, outcomes, and missing outcome data using standardized and pretested data extraction forms with instructions. Before starting data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. We will contact study authors to resolve any uncertainties. Disagreements will be resolved by consensus with any unresolved issues referred to another reviewer [7, 8].

Data synthesis

We will conduct analyses for each anti-inflammatory drug and for each outcome of interest. We will determine the confidence in estimates for each body of evidence and conduct an analysis for the body of evidence that warrants greater confidence.

For trials that report dichotomous outcomes, we will calculate the pooled relative risk with associated 95% confidence interval (CI). For continuous outcomes, we will use weighted mean differences (WMD) and its 95% CI as effect measure after we convert them into same scale. Once the WMD has been calculated, we will contextualize this value by noting, when available, the corresponding anchor-based minimally important difference (MID), the smallest change in instrument score that patients perceive is important.

Ethics and dissemination

Ethical approval is not needed for a systematic review that does not involve privacy concerns due to collection or presentation of data from individual patients. The systematic review will be submitted to journals and presentations with scores in related research conferences [7].

Evolution Studies

Radio-labelled erythrocytes

Later volunteer studies investigated the effects of drugs on gastric mucosal bleeding using radio-labelled red blood cells. Labelling is relatively simple; red cells are incubated *ex vivo* with chromium and then re-injected into subjects. Initially, the bleeding detected was assumed to come from the stomach. Subsequently, it has become clear that this measure reflects whole gut blood loss and it has been revived for this purpose. Early studies also suggested that some results might have been spurious as some chromium is detached from red cells and excreted in the bile. Aspirin influences biliary flow, and could conceivably give false results.

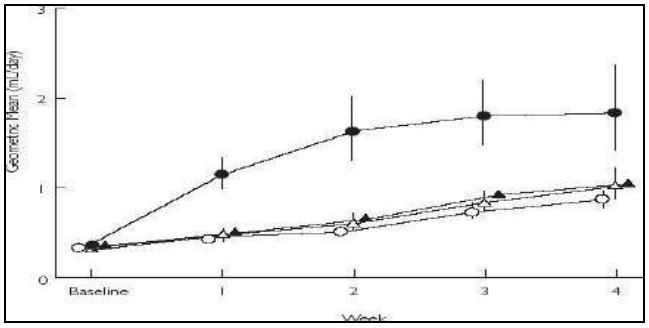

Fig 2: Geometric mean daily faecal blood loss, calculated using [5] chromium-labelled erythrocytes, with 84% confidence intervals with permission. Placebo (○); Rofecoxib 50 mg (▵); Rofecoxib 25 mg (▲); Ibuprofen 2400 mg (•).

Gastric washings

A more direct approach to acute mucosal bleeding involved measurement of microscopic blood using the peroxidase activity of haemoglobin in timed gastric washings. After a period of aspirin ingestion, gastric juice is washed and aspirated through a Salem sump orogastric tube. Gastric mucosal bleeding is assessed by adding aliquots of gastric aspirate to citrate buffer and Orth tolidine in cuvettes, with hydrogen peroxide (20 volumes per 100 ml) added after 45 s. The peroxidase activity of haemoglobin liberates oxygen from hydrogen peroxidase, which oxidizes Orth tolidine to a blue colour. This is then quantified spectrophotometrically 30 and 60 s after the addition of hydrogen peroxide. Two days treatment with aspirin 600 mg twice daily increased mucosal blood loss by a factor of 9.3 ($P < 0.001$) in one study compared with placebo. The sensitivity threshold for blood detection was determined *in vitro* as 2 µl l^{-1}Nevertheless, they are not as effective in reducing gastrointestinal complications as is the substitution of the standard NSAID with a COX-2 inhibitor in the acute situation [7, 8].

Volunteer endoscopy

This direct approach to the assessment of acute mucosal injury was pioneered by Lanza. In a series of painstaking endoscopic studies in which Lanza himself conducted virtually all the endoscopies, he showed that aspirin and non-aspirin NSAIDs caused acute mucosal erosions, although some NSAIDs such as norboletone, etodolac and oxyproline did not. However, other studies showed that azapropazone caused little acute injury, whilst subsequent epidemiological data showed this drug was particularly associated with ulcer haemorrhage. Thus, these studies suggested that acute endoscopic studies were not particularly valuable in predicting which of the nonselective NSAIDs would be safer than others in clinical practice [5].

Volunteer COX-2 studies

Acute volunteer studies show consistently that COX-2 inhibitors even at an exceptionally high dose do not cause any erosions compared with placebo. This is not surprising since the drugs lack an intrinsic mechanism for inducing toxicity. By contrast, studies of NSAIDs with high dose H_2-receptor antagonists or PPIs nonprescribed (which is probably as effective as use of COX-2 inhibitors in patient studies) generally still show some persisting erosions, although the number is reduced. Although seldom compared directly, prostaglandin analogues such as misoprostol generally result in fewer erosions than an acid suppressive regime during NSAID treatment, a result that is interesting as long-term studies suggest that acid suppression may be more effective against ulcers and less effective against erosions compared to misoprostol. Recently, a third protective strategy has been assessed with the use of nitric oxide (NO)-donating NSAIDs, otherwise known as cyclooxygenase inhibiting NO-donators (CINODs). These drugs have been very effective in animal models. In human studies, the CINOD AZD3582 (NO-naproxen) behaved like a combination of an NSAID with a PPI in showing reduced but not absent erosions [1, 2].

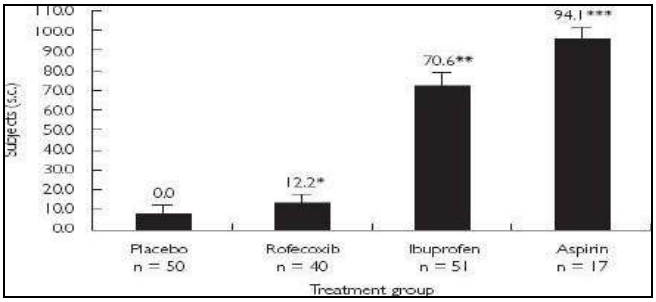

Fig 3: Percentage of subjects with a maximum gastric or duodenal lesion score = 2. (*, $P = 0.525$ *vs* placebo. **, $P < 0.001$ *vs* placebo and forecoxa. ***, $P < 0.001$ *vs* placebo and forecoxa (MK-0966); $P = 0.054$ *vs* ibuprofen).with permission.

Protection with proton pump inhibitors

The use of PPIs as NSAID prophylaxis has been extensively investigated in chronic patient studies. These have included primary prophylactic studies of patients that did not have an ulcer at baseline [6,7], pragmatic prophylactic studies in which there was no baseline endoscopy [2,3] and secondary prophylactic studies in which patients found to have an ulcer at initial endoscopy underwent a course of healing before randomization to maintenance treatment [1,2]. All of these studies have been consistent in showing a reduction in NSAID ulceration of approximately three-fold in patients taking PPIs compared with placebo, with reductions in NSAID-associated symptoms as well.

Histamine 2-receptor antagonists

Histamine 2-receptor antagonists (H_2RAs), which inhibit acid secretion, have also been evaluated for reducing NSAID-associated complications. A meta-analysis of 14 trials found that H_2RAs (eg, famotidine and ranitidine) were protective at high doses, but at commonly prescribed doses they reduced the risk of duodenal but not gastric ulcers.[8]

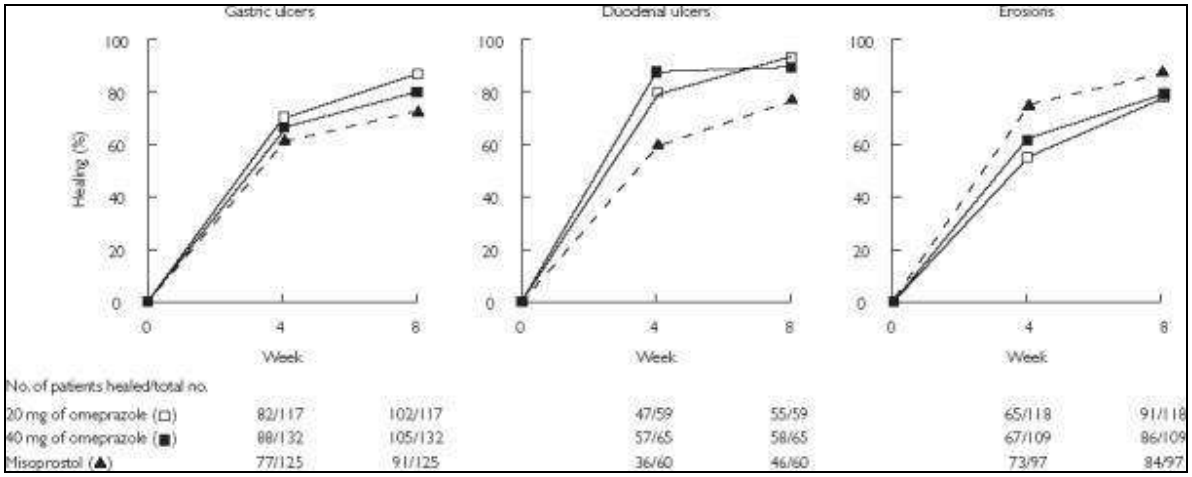

Fig 4: Cumulative healing rates of gastric ulcers, duodenal ulcers, and erosions at 4 and 8weeks during treatment with 20 mg omeprazole daily, 40 mg omeprazole daily, or 200 µg misoprostol four times daily From [9].

Misoprostol protection

Most studies of misoprostol cop escribed with NSAIDs have been in patients with an undamaged mucosa at baseline. In these studies, patients who are already using NSAIDs typically undergo a washout period, or those who start NSAIDs are assessed by prior endoscopy. Patients with osteoarthritis are usually studied, although sometimes a mixed population or those with rheumatoid arthritis comprise the study group. Patients typically undergo endoscopy at baseline and after 13 weeks, often with an interval endoscopy in between. It is important to realise that those with interval endoscopies report a cumulative ulcer incidence, which is, for obvious reasons, higher than those with an endoscopy at the end of the study. misoprostol (200 mg twice daily) did less well than those managed with omeprazole 20 mg with regards ulcer recurrence or symptoms [6, 7].

Testing Methods

Population. The intake of these pharmaceutical compounds leaded to significant levels of them and their metabolites to be found in the environment [7, 8] as well as in the wastes of the cities. European Union (EU) recommendations advise to validate the analytical methods at different levels of verifica-tion and achievements considering of relevance the existence of inter-laboratory exercises in order to show the goodness and robustness of the analytical methodologies. The results of a collaborative inter-laboratory exercise for the analysis of NSAIDs in environmental samples have been recently pub-lished [9]. In this study, fourteen laboratories belonging to EU countries (Austria, France, Germany, Greece, Italy, Slovak Republic, Slovenia, Spain, and Switzerland) partici-pated. River and wastewater samples were analyzed using solid phase extraction (SPE) as sample pre-treatment step and then Mass Spectrometry (MS) coupled to liquid chroma-tography (LC) or gas chromatography (GC) was employed for the determination of the analytes. A good agreement among the results of the laboratories involved in the exercise was found. The outliers and discrepancies were higher for wastewater compared to river water and also higher for GC compared to LC. These facts are attributed to the com-plexity of the matrices and also to the additional derivati-zation step required for the GC analysis. The results of a second inter-laboratory exercise reveal the importance of the preservation of the samples on dry ice in order to reduce the number of outliers [10]. Population. The intake of these pharmaceutical compounds leaded to significant levels of them and their metabolites to be found in the environment [7, 8] as well as in the wastes of the cities. European Union (EU) recommendations advise to validate the analytical methods at different levels of verifica-tion and achievements considering of relevance the existence of inter-laboratory exercises in order to show the goodness and robustness of the analytical methodologies. The results of a collaborative inter-laboratory exercise for the analysis of NSAIDs in environmental samples have been recently pub-lished [9]. In this study, fourteen laboratories belonging to EU countries (Austria, France, Germany, Greece, Italy, Slovak Republic, Slovenia, Spain, and Switzerland) partici-pated. River and wastewater samples were analyzed using solid phase extraction (SPE) as sample pre-treatment step and then Mass Spectrometry (MS) coupled to liquid chroma-tography (LC) or gas chromatography (GC) was employed for the determination of the analytes. A good agreement among the results of the laboratories involved in the exercise was found. The outliers and discrepancies were higher for wastewater compared to river water and also higher for GC compared to LC. These facts are attributed to the com-plexity of the matrices and also to the additional derivati-zation step required for the GC analysis. The results of a second inter-laboratory exercise reveal the importance of the preservation of the samples on dry ice in order to reduce the number of outliers [10]. Population. The intake of these pharmaceutical compounds leaded to significant levels of them and their metabolites to be found in the environment [7, 8] as well as in the wastes of the cities. European Union (EU) recommendations advise to validate the analytical methods at different levels of verifica-tion and achievements considering of relevance the existence of inter-laboratory exercises in order to show the goodness and robustness of the analytical methodologies. The results of a collaborative inter-laboratory exercise for the analysis of NSAIDs in environmental samples have been recently pub-lished [9]. In this study, fourteen laboratories belonging to EU countries (Austria, France, Germany, Greece, Italy, Slovak Republic, Slovenia, Spain, and Switzerland) partici-pated. River and wastewater samples were analyzed using solid phase extraction (SPE) as sample pre-treatment step and then Mass Spectrometry (MS) coupled to liquid chroma-tography

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pated. River and wastewater samples were analysed using solid phase extraction (SPE) as sample pre-treatment step and then Mass Spectrometry (MS) coupled to liquid chroma cograph (LC) or gas chromatography (GC) was the most frequent sample pre-treatment procedure for the analysis of NSAIDs [9, 10].

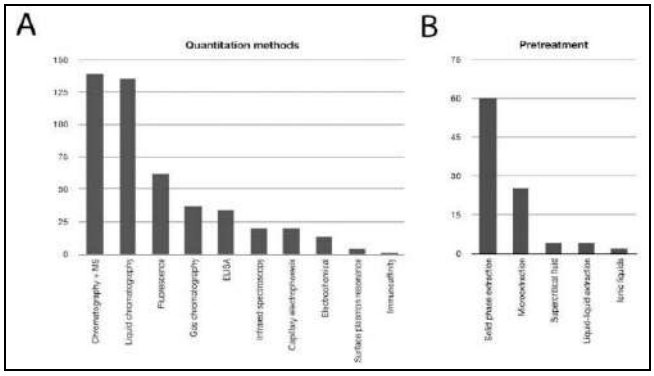

Fig 6: Figure showing the outcome of a survey of the research and dealing with analytical methods employed for quantitation of NSAIDs.

Sample pre-treatment procedures

The nature of the sample's matrix in which NSAIDs can be found is very disparate, taking into account their level concentration, the presence of interferents and/or whether the sample is solid or liquid. Thus, the pre-treatment required for the determination of NSAIDs in biological or environmental samples is quite different compared to that for the case of pharmaceutical products.

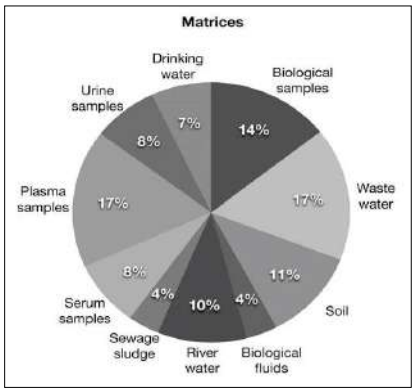

Fig 7: Nature of the matrices in which NSAIDs are most frequently quantified, according to the literature survey conducted.

Conclusions

The huge disparateness of the matrices in which NSAIDs can be found, makes it necessary to use different pre-treatment procedures, adequate to extract, pre-concentrate and clean-up every analyte from each type of matrix [7,8].

Herein, for the analysis of NSAIDs in pharmaceutical products, biological samples, foods, and environmental samples, we have reviewed the most common pre-treatments (i.e. LLE and SPE) as well as the most sophisticated, environmentally friendly new trends: LLME (DLLME, HFLPME) and SPME. Furthermore, we have discussed the most widely employed separation and quantitation techniques for these pharmaceuticals, mainly LC, GC, CE using UV-Vis, FD, MS, and the tandem MS/MS as the most powerful tool among them [10].

1) Decrease solvent volume and time consumption for a greener, faster, cheaper analysis;
2) Multi-residue analysis, because these compounds are usually accompanied by other pharmaceuticals and different emerging pollutants;
3) Automation of the analytical steps, from the pre-treatment to the quantitation of the analytes.

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