EXPERT REVIEWS

The potential and promise of mefenamic acid

Expert Rev. Clin. Pharmacol. 6(3), 289–305 (2013)

Nevio Cimolai

Department of Pathology and Laboratory Medicine, Children's and Women's Health Centre of British Columbia, Vancouver, BC, V6H 3V4, Canada
Tel.: +1 604 271 9321
Fax: +1 604 271 9321
ncimolai@mail.ubc.ca

Clinical use of mefenamic acid has generally declined in an era where other NSAID use has flourished. While having modes of action and general toxicities similar to other NSAIDs, mefenamic acid, as a member of the fenamates, nevertheless possesses some unique *in vitro* effects that have the potential to distinguish this agent from others. Use of this drug remains relevant for pain syndromes and some gynecological disorders, albeit with considerable competition from other NSAIDs. New basic science has considerably improved the understanding of the biochemistry of mefenamic acid. As well as maintaining its use in traditional settings, there is a tremendous potential for expanding the application of mefenamic acid to niche roles.

Keywords: analgesia • anti-inflammatory • mefenamic acid • pharmacology • toxicity

Mefenamic acid is an anti-inflammatory analgesic, which has enjoyed considerable use over the last half-century. As new anti-inflammatory and analgesic medications have become available, the use of mefenamic acid has considerably declined. Herein, the history, pharmacology, uses and adverse effects of mefenamic acid are reviewed.

General considerations

Mefenamic acid is a weak organic acid. In particular, it is structured as a *N*-(2,3-xylyl) anthranilic acid and is not a particularly complicated molecule (Figure 1). Interestingly, this drug shares relatedness to 3-hydroxyanthranilic acid, a naturally occurring metabolite of tryptophan. It was initially released as early as 1962 for pharmaceutical purposes and was largely marketed then by Parke, Davis and Company (NJ, USA) in most countries under the names of Ponstan® and Ponstel®. In the laboratory, it is a derivative of *N*-phenylanthranilic acid and it is a member of the 'fenamate' family of NSAIDs (one of five broad families of such agents including salicylates, indoleacetic acid analogs, acylpropionic acid congeners, fenamates and coxibs). The drug was known very early to possess anti-inflammatory, analgesic and antipyretic properties [1].

Winder has written on the evolution of fenamates, indicating that they were developed in the 1950s when "there were striking evidences that the management of inflammatory conditions was breaking out of the old salicylate mould" [1]. With the availability of corticosteroids, salicylates and phenylbutazone, laboratory (mainly animal) models of inflammation were established that could allow for the investigation of other new compounds. Human pain models were established for assessing mefenamic acid and similarly acting agents, but the sole use of prostaglandin inhibition *in vitro* was not sufficiently specific [2]. With the emergence of knowledge that mefenates were distinctly separable in effect from corticosteroids, but significantly resembling salicylates and phenylbutazone, hundreds of mefenates were synthesized and assessed. Mefenamic acid and a few other mefenates emerged for clinical trials. When clinical use emerged in the 1960s, there was reservation about using mefenamic acid for prolonged periods owing to its (mainly gastrointestinal) side effects. For example, the Medical Letter on Drugs and Therapeutics (1967) concluded that, "In view of the limited knowledge of the effects of mefenamic acid, if it cannot safely be used for more than 7 days, it should not be used at all" [3].

Mefenamic acid is highly cited in the existing scientific and medical literature, and the mefenates are among the most highly studied existing pharmacological agents. Soon after mefenamic acid became available for public use (1963), it was one of the most highly prescribed medications. In the 1990s, it was ranked by some as being among the top three NSAIDs prescribed [4]. For example, in the UK alone, nearly two million prescriptions of mefenamic acid were made yearly at one time [5]. In a general medical services plan in Ireland, the estimated utilization was approximately 3.99 daily

 10.1586/ECP.13.15 ISSN 1751-2433

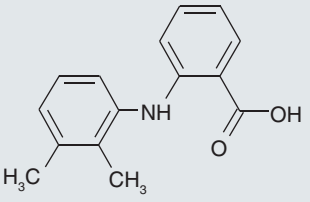

Figure 1. Mefenamic acid.

doses per 1000 population per day [6]. American data from 1983 estimated prescriptions to tally approximately 700,000. During the last decade, although it is apparent that the total number of mefenamic acid prescriptions has declined, worldwide use continues [7]. A recent study from Malaysia finds that mefenamic acid and diclofenac were the most commonly prescribed NSAIDs [8].

As a correlate of the latter use, several investigators have found that mefenamic acid is detectable in waste and ground water [7,9]. The finding of this drug in bovine milk is also cited [10].

Potential uses of mefenamic acid abound, as the author later illustrates, but despite potential generalized use for pain treatment, mefenamic acid was not uncommonly reserved for ameliorating menstrual pain [11]. Perhaps a large part of the reasoning for the latter was the eventual availability of numerous other antinociceptive (mainly NSAID) compounds. As late as the last decade, some concluded that mefenamic acid could not be seen as an agent that was superior to other NSAIDs, although diverse usage was possible [12].

Physiology

Whereas physiological effects of mefenamic acid are critical to the understanding of its properties that strike to the heart of its current clinical uses, there is an impressive plethora of studies, both *in vivo* and *in vitro*, that illustrate the potential diversity of effects that mefenamic acid may have on the body (**Box 1**). Such a diversity of physiological effects explains why there is reason to believe that mefenamic acid is a very unique NSAID, and that, while clinically it may have no major benefit over many other NSAIDs when used for anti-inflammatory, antipain and antipyretic purposes, it may prove to have future benefits in areas yet to be realized, whether alone or in combination with other pharmaceuticals. It is also impressive that many such physiological research papers continue to be published despite the availability of mefenamic acid for research now some 60 years after its creation.

As gleaned from the myriad of enzymatic modulations, mefenamic acid's effect on the body may be complex. Apart from several direct antienzyme activities, it can generally inhibit and uncouple oxidative phosphorylation. It can also inhibit the hepatic CYP1A2 enzyme. Whereas these attributes may be appreciated at concentrations *in vitro* that are similar to circulating drug levels, mefenamic acid can also achieve high intracellular concentrations. These and other molecular physiological and biochemical effects may give credence to mechanisms of hepatic and renal changes that can be experienced during use. Perhaps it is surprising that, at clinically effective doses and blood levels, more adverse reactions have not occurred.

Likewise, mefenamic acid has considerable and diverse effects on cellular ion channels. This effect is mostly documented for cation channels. Accordingly, such effects have relevance to cellular transport systems for cations and several other molecules. The drug does not appear to be cytotoxic *in vitro*, although lactic acid production is increased in tissue culture cells. It can enhance cytotoxicity of some chemotherapeutic agents. Intestinal fluid movement and membrane integrity can become altered. The agent was found to have a general antiproliferative effect on colonic cancer cells *in vitro* [13], and an antimetastatic effect in an animal model of lung cancer. An antimitotic effect has been previously shown [14]. Although again of possible importance to mechanisms of action or mechanisms of toxicity, these attributes may now pave the way for new avenues of pharmacological manipulation and benefit.

Mefenamic acid can be a competitive inhibitor at protein- and receptor-binding sites. In so acting, it can displace molecules such as thyroxine, uric acid and warfarin from protein carriers. Although COX inhibition is regarded as a crucial factor in the anti-inflammatory effect of the drug, inhibition of PGE2 binding to its receptors in a dose-dependent fashion has also been cited.

As prostaglandin synthetase inhibition was becoming recognized as a major mechanism of action for NSAIDs, evidence for mefenamic acid's role in the same mode of action was affirmed [15,16]. Mefenamic acid was as potent as, or more than, most other NSAIDs [16]. By the early 1990s, the COX1 and COX2 isomorphs of the cyclo-oxygenase enzyme for prostaglandin synthesis were acknowledged, and thereafter, an understanding of their complex interdependency and interactions emerged. Ultimately, the potential for differential COX1 and COX2 activity would be seen as a focus towards selecting NSAIDs with varying toxicity and/or efficacy. Although the differentiation of COX selectivity could be methodology dependent, mefenamic acid was deemed to be a competitive, time-dependent and reversible inhibitor for both COX1 and COX2 [17]. Competing views were nevertheless published [17–19]. For example, one study found mefenamic acid to be a potent and preferential inhibitor of COX1, although not being COX1 selective [17]. Another study found the IC_{50} for COX1 inhibition to be approximately 8–10 times lower than for COX2 [19]. In yet another setting, mefenamic acid was shown (along with diclofenac) to be COX2 selective using conventional NSAID-selectivity indexing [18]. Despite this, the same authors concluded that, while the drug could have COX2 selectivity on a proportionate basis, it could still maintain enough COX1 activity that sufficient biochemical activity, and hence consequent clinical symptoms, could occur in regards to gastric PGE_2. That is, gastric side effects could be predicted despite what *in vitro* would appear as COX2 selectivity. Indeed, mefenamic acid was found to yield gastrointestinal erosions at a similar frequency to other agents that would be deemed as relatively non-COX2 selective [20].

Mefenamic acid can exert variable immunological effects including immune modulation [21–23]. The latter can include effects on phagocytosis and immune cell migration. The direct interaction of such changes with cyclo-oxygenase inhibition is not yet fully understood, but there remains the possibility that anti-inflammatory effects may include more than can be obtained if it were solely through the impact on prostaglandin pathways. Under some circumstances, mefenamic acid may accentuate histamine release [24], although it may inhibit tachyphylaxis to histamine in a dose-dependent manner.

Mefenamic acid has an effect on platelets, such as inhibition of platelet aggregation [25]. It may also have fibrinolytic activity, while nevertheless stabilizing hemolysis. Subsequent studies demonstrate inhibition of atheromatous plaque formation and atherogenesis *in vivo* [26,27].

A key to potential clinical uses for mefenamic acid appears to rely in part on its ability to affect smooth muscle. It can decrease uterine resting pressure and also has a dose-dependent effect for relaxing tonic uterine contraction. It can reduce arterial constrictions induced by norepinephrine or photoactivation. Effects on tracheal smooth muscle, gastric muscle and bowel transit time have been reported. Both mesenteric vein and renal blood flow can be modulated [28,29]. There may be a direct acceleration of bowel transit time.

Various nervous system actions have been assessed, and while mefenamic acid can be neurotoxic [30], it has potential for neuroprotection [30–32]. Among the latter is the spectre of protecting the hypoxic brain [33]. GABA-receptor modulation and activation have been found [30].

In experimental results, mefenamic acid can protect the hypoxic brain, although this has been disputed by some [34,35]. *In vivo*, mefenamic acid can protect animals from pilocarpine-induced seizures [36]. In an animal model of Alzheimer's disease equivalent, the drug could attenuate deleterious changes [37]. Mefenamic acid, like other NSAIDs, can decrease pyrogen effects.

Metabolism, excretion & kinetics

In its acidic form, mefenamic acid is poorly soluble, but it could be much more soluble in its sodium salt. Nevertheless, up to 80% of an oral ingestion of mefenamic acid is absorbed. Unconjugated drug achieves peak blood levels of 2–6 mg/l (250-mg dose) and 4–24 mg/l (500-mg dose) after 2–4 h [38,39]. The half-life is approximately 2–4 h, and blood levels are less than 0.1 mg/l after 24 h. There is very little data on the use of this agent during renal failure, but dosage adjustment during renal failure for short-term use does not appear to be necessary.

Mefenamic acid is largely metabolized by the liver via oxidation processes that utilize the cytochrome mono-oxygenase P450TB, CYP2C [40]. Simple Michaelis–Menten kinetics are observed. Most NSAIDs are metabolized by such enzymes, but mefenamic acid has a much higher affinity than other NSAIDs. A 3-hydroxymethyl metabolite is most common, and a 3-carboxyl metabolite is less evident. Enzyme analogues to UDP-glucuronyltransferases are responsible for creating acyl glucuronides from mefenamic acid and its two major oxidized metabolites [41]. The glucuronides achieve peak blood levels by 2–6 h and

Box 1. Physiological effects described for mefenamic acid.

Competitive displacements
- Can generally displace other pharmacological agents from albumin binding sites
  - Specifically, can displace warfarin and uric acid from albumin
- Increases free thyroxine in serum
- Inhibits PGE_2 binding to receptor in dose-dependent fashion
- Dose-dependent inhibition of prolactin binding
- Increases estrogen binding capacity
- Displaces thiopental from protein

Transport systems
- Inhibits adenosine transport
- Affects liver sulfate transport
- cAMP inhibition
- Effect on glutamate/glycine transporter
- Inhibits T3 uptake by hepatocytes
- Affects ion transport in tracheal epithelial cells

Permeability and ion channels
- Selectively inhibits some Ca^{2+} channels
- Agonist and inhibitor for some cation channels (e.g., slo2.1)
- Activates receptor-based cation channels in smooth muscle
- Achieves a high intracellular concentration
- Inducer of rat renal cortex mitochondrial permeability

Cellular stability
- Increases lactic acid in tissue culture cells
- Increases small bowel permeability
- Affects intestinal fluid movement and membrane integrity
- No effect on frog cardiac pacemaker cells
- Decreases metastatic lung cancer in mice when given with chemotherapy
- Protects the hypoxic heart
- Antimitotic effect
- Generally not cytotoxic at concentrations achieved *in vivo*
- Toxic to hepatocytes *in vitro*
- Enhances cytotoxicity of chemotherapeutic agents *in vitro*
- Affects colonic cancer cell proliferation
- Can cause liver cancer cell apoptosis

Effects on enzymes and synthesis
- Inhibits fibroblast hyaluronic acid production
- Inhibits melanin synthesis
- Antiproteolytic *in vitro*
- Antilipase activity *in vitro*
- Inhibits bisphenol biotransformation
- Affects cholinesterase
- Inhibits calmodulin-stimulated phosphodiesterase
- Inhibits tyrosinase protein level
- CYP1A2 enzyme inhibition
- Inhibits liver sulphotransferase
- Activator of AMP-protein kinase
- Renal enzyme inhibition
- Inhibits liver UDP-transferase

Box 1. Physiological effects described for mefenamic acid (cont.).

- Inhibits glucuronidation
- Inhibits/uncouples oxidative phosphorylation
- Inhibits ATP synthesis in rat kidney
- Inhibits methyltransferase
- Inhibition of amine decarboxylases
- Inhibits chymotryptic hydrolysis
- Decreases peroxidase oxidation
- Inhibits caspase 3-like activity of gastric mucous cells
- Pro-oxidant catalytic activity
- Inhibits myeloperoxidase
- Inhibits folate-dependent enzymes
- Inhibits phospholipase enzymes
- Inhibits some liver oxidation functions
- Inhibits cartilage phosphodiesterase
- Increases mitochondrial ATPase activity
- Affects TRPM3 channels that modulate glutamatergic transmission in the brain

Anti-inflammatory

- Generally anti-inflammatory
- Initially generally believed to inhibit prostaglandin synthetase
- COX1 and COX2 inhibition specifically
- Decreases intrauterine prostaglandin levels
- Antagonizes prostaglandin endoperoxidases and prostaglandin effects in the myometrium
- Decreases inflammatory protein intraperitoneally

Allergy and immunity

- Accentuates histamine release
- Enhances the reactivity of the allergic-sensitized lung
- Inhibits release of aorta contracting substance during anaphylaxis
- Potentiates passive cutaneous IgE-dependent anaphylaxis
- Dose-related inhibition of tachyphylaxis to histamine
- Immune modulation
- Effects on neutrophil enzyme release
- Blocks cold-stress neutrophil response
- Affects L-selectin in neutrophils
- Dose-dependent decrease in adjuvant arthritis
- No affect on the Arthus reaction
- Effect on monocyte migration and phagocytosis

Thrombosis and atherogenesis

- Enhances thrombosis after photoactivation
- Fibrinolytic activity
- Platelet effects including inhibition of platelet aggregation
- Stabilized heat-induced hemolysis
- Inhibits macromolecule-induced red blood cell aggregation *in vitro*
- Inhibits atherogenesis *in vivo*
- Inhibits atherosclerotic plaque formation
- Can alter the antiplatelet effect of acetylsalicylic acid

Smooth muscle and related effects

- Relaxes mesenteric arteries

are more avidly bound to albumin. These conjugates are major urinary metabolites. Fecal excretion of mefenamic acid is anticipated given the lack of full absorption, but metabolites are rare in feces. Not all oxidation metabolites in the blood and urine are conjugated, and some minor enterohepatic circulation probably occurs [38]. In the newborn, the same metabolites are found, but proportionately less metabolite concentrations arise due to the immature capability of the newborn liver. The longer half-life becomes normalized in approximately 1 month after birth.

When coingested with water, oral absorption is reduced, but food does not appear to have the same effect [42]. Small amounts of mefenamic acid enter breast milk (0.04–0.033 mg/l). Diabetes can affect bioavailability and kinetics [43]. Magnesium hydroxide-based antacids increase mefenamic acid absorption, but aluminum hydroxide (and kaolin) bind it.

The drug has been available in capsules and film-coated tablets. Variation in absorption has been determined among capsules and between capsules and tablets [39,44]. Variation in tablet stability has been shown [45]. Sustained-release forms in alginate capsules have attracted attention, but no such commercial preparations have been commercialized. Overall, mefenamic acid has been classified as intermediately soluble but highly permeable (Class II) [46]. Both intestinal pH and bile can have significant impact on absorption. Release from acrylate bone cement has also been studied [47]. Two major crystal polymorphs are recognized, but the clinically available drug exists mainly in 'form I' [48].

Given the poor solubility, some have assessed the potential for esters or other conjugates [49,50]. Topical formulations have

Box 1. Physiological effects described for mefenamic acid (cont.).

- Effects on renal blood flow
- Dose-dependent relaxation of tonic uterine muscle contraction
- Dose-dependent decrease in muscle tone in trachea and gastric muscle
- Decreases uterine resting pressure
- Enhances food-related blood flow to intestines
- Accelerates bowel transit time
- Reverses mesenteric artery constriction during bacteremia
- Antagonizes bronchoconstriction caused by kinins
- Decreases norepinephrine-induced aortic ring constriction
- Decreases photoactivation-induced arteriolar constriction

Neuroprotection

- Hypoxic brain protection
- Taming effect on septal syndrome
- Affects postsynaptic currents
- Can be neurotoxic at high doses
- GABA receptor modulation and activation
- Affects the CNS actions of methionine
- Antagonizes D-serine-induced neurotoxicity

Other

- Protects hypoxic heart experimentally
- Quenches and scavenges nitric oxide radicals
- Antipyrogen effect

also attracted attention [51,52]. Metal complexes of mefenamic acid maintain biological activity. Given the success of mefenates, structural analogues continue to attract attention [53,54].

Uses

Premenstrual syndrome

Two studies have concluded that mefenamic acid is beneficial for women who suffer from premenstrual syndrome (e.g., $p < 0.001$ vs placebo for premenstrual symptoms) [55,56]. A double-blind placebo-controlled trial, however, did not find any benefit of mefenamic acid over placebo [57].

Menorrhagia

As a group, NSAIDs are accepted as pharmacological agents that reduce menstrual flow in patients who suffer from menorrhagia when compared with placebo [58], and several studies have confirmed the same for mefenamic acid [59,60]. Such evidence has led many primary care physicians to implement mefenamic acid as one standard of treatment for menorrhagia [61].

For this purpose, mefenamic acid doses of 500 mg thrice daily during menses (typically 3–5 days) have been used. The reduction in menstrual flow varies considerably from 2 to 78%, but typical reductions range approximately 25–40% [59,62–70]. For academic purposes, menorrhagia is defined as blood loss greater than or equal to 80 ml during a menstrual cycle. In studies of mefenamic acid use, it is apparent that a greater percentage reduction is achieved for those with a greater degree of menorrhagia [59,62,71]. The drug also reduces the total days of menstrual flow [59,60]. An effect was achieved both for primary menorrhagia and for those with apparent pelvic disease (e.g., fibroids) or coagulation disorders [72]. When assessed over the long term as late as 6–15 months, the beneficial effect of the drug was preserved [73].

The histopathology of drug action has been studied with uteri that were removed from women with or without preceding treatment. Uteri from females having received mefenamic acid demonstrated more frequent blood vessel closure and increased vasoconstriction [63]. The drug reduces endometrial prostaglandins E and F; these prostaglandins are in high concentration within the endometrium of patients who suffer menorrhagia [74].

There is meagre evidence to suggest that mefenamic acid is better than other NSAIDs [58,65]. The agent is comparable with oral contraceptive therapy [68]. Tranexamic acid, danazol and intrauterine hormonal devices are more efficacious, albeit with a trade-off in side effects [58,66,69,70].

Pain syndromes

Early studies found that mefenamic acid could ameliorate chronic pain of multiple etiology [75]. Indeed, pain threshold experiments confirmed the value of this drug over placebo [76].

Primary dysmenorrhea

Dysmenorrhea is considered primary when there is no evident organic cause for the pain, although there is no absolute pain threshold that can be defined scientifically. Doses of 250–500 mg thrice-daily or four-times daily are associated with significant reductions of pain in up to 75–90% of the patients in open studies [71,77]. When compared with placebo, mefenamic acid is unequivocally superior in relieving dysmenorrhea [78–85]. These findings have been accumulated from open studies, single-blinded studies and double-blinded crossover studies.

A review of trials up to the early 1980s concluded that the fenamate family of drugs was superior to ibuprofen, naproxen and indomethacin [86]. Focused studies found mefenamic acid to be equivalent to ibuprofen, naproxen, ketoprofen, piroxicam and meloxicam [84,87–90]. Mefenamic acid was superior to the combination of dextropropoxyphene and paracetamol [91]. One report suggests superiority of etoricoxib, but drug dosages were not detailed [92]. Another report proposed equivalency of mefenamic acid, ibuprofen and a ginger root powder formulation [93].

Along with the reduction of pain, mefenamic acid decreased uterine tone and frequency of uterine contractions [94]. *In vitro*, mefenamic acid can block the increased uterine contractility that is stimulated by prostaglandin endoperoxide analogues [95].

Other gynecological & obstetrical uses

Mefenamic acid can reduce pain caused by secondary dysmenorrhea [84,96]. The drug reduced blood loss associated with intrauterine devices [80,97,98]. It could also modulate blood loss associated with depot progesterone in the short term, albeit not in the long term [99]. As a premedication, mefenamic acid reduced pain that was associated with hysteroscopy, uterine curettage and infusion sonohysterography [100–103]. It was better than placebo in reducing premature labor in those at risk, but such a benefit must be tempered with the potential effect of this drug on the ductus arteriosus [104].

Musculoskeletal injury

For musculoskeletal injuries that are attended to in the ambulatory emergency setting, mefenamic acid proved to diminish pain analogous to other NSAIDs, paracetamol and propoxyphene/paracetamol [105–108]. Such benefit was also demonstrated specifically for patients with Colles' fracture [109]. Soft-tissue injuries also respond to mefenamic acid [110].

Patients with acute back pain in the ambulatory setting benefit from mefenamic acid as assessed by both physicians' and patients' pain ratings [111,112]. One of these assessments found that this drug was chosen more often than other comparators for this purpose at the time [112].

Osteoarthritis

Several studies have found that mefenamic acid can be equivalent to or better than other NSAIDs for chronic osteoarthritis, including the elderly (e.g., $p < 0.005$ vs placebo for pain relief score; p = not significant vs indomethacin) [87,113–118]. The latter studies have generally used dosages of 500 mg, three-times daily.

Endodontic pain

Mefenamic acid has been assessed in double-blind, placebo-controlled trials for the relief of postsurgical dental pain. In

doses of 250 mg every 4–6 h after surgery, it is superior to placebo and also to a lesser extent superior to acetylsalicylic acid (ASA; 600 mg every 4–6 h; e.g., $p < 0.01$ vs placebo for pain relief scores) [119–121]. The combination of ASA and mefenamic acid was found to be superior to either alone [121]. In other similar studies, mefenamic acid was comparable in efficacy with piroxicam alone or ibuprofen, paracetamol and codeine in combination [122,123].

Headache

Early study of mefenamic use for migraine headache found benefit but of variable degree [124]. A beneficial effect for tension headache was also noted [125]. In a placebo-controlled trial, mefenamic acid provided significant relief for migraine [126], but minor benefit over the use of acetaminophen [127]. The latter is consistent with the use of other NSAIDs for migraine. A few studies suggest the potential use of mefenamic acid for migraine prophylaxis analogous to the use of propranolol [128,129].

Postoperative pain

Among various postoperative pains, mefenamic acid has an analgesic effect, including when it was used after episiotomies [130,131]. It was not effective, however, for pain from panretinal photocoagulation [132].

Other chronic pain

Mefenamic acid has proved beneficial for the treatment of chronic pain of bone, muscular, neuropathic and other soft tissue diseases [75,118,133–135]. One study suggested that mefenamic acid was not effective for 'organic bone disease' of variable etiology [118]. Other studies suggested that it was of value for many patients who suffered from chronic pain of malignancies (e.g., $p < 0.05$ vs placebo for pain relief) [134,135]. Generally, doses of 500 mg three times per day were employed in such studies.

Rheumatoid arthritis

A beneficial effect of mefenamic acid over placebo for patients suffering from rheumatoid arthritis was apparent (e.g., $p < 0.025$ vs placebo for both grip strength and walking time) [136–138]. In total doses of 1 and 1.5 g per day, mefenamic acid has equivalence to many other NSAIDs (e.g., p = not significant vs ibuprofen in pain chart scores) [137–141]. Measures of benefit for the latter studies have variably included subjective pain scores, articular indices, morning stiffness degree, joint tenderness, grip strength and walking time.

Pediatric use

The potential value of mefenamic acid in pediatric care was recognized early, and the drug has been especially evaluated as an antipyretic [142–144]. Effective doses are generally in the range of 3–6 mg/kg.

A more focused use of mefenamic acid for patent ductus arteriosus in newborns, especially those premature, has been detailed largely from Japan [145–147]. In a dose of 2 mg/kg every 12–24 h, mefenamic acid was reasonably efficacious in achieving ductal closure [147–149]. The kinetics of mefenamic acid in such patients has been observed [145]. When indomethacin-treated patients have ductal reopening, mefenamic acid has been found to achieve secondary closure in some patients [146]. Along the same mechanism, mothers who have received mefenamic acid late in pregnancy can harm their babies owing to premature ductal closure when the babies are yet dependent on intrauterine open-ductal circulation [150,151].

Asthma

Case reports highlight the ability of mefenamic acid to mitigate asthma, as measured by increases in forced expiratory volume in 1 s and peak expiratory flow rates [152,153]. A case series has also proposed the potential benefit of mefenamic acid in patients with chronic bronchial asthma with pulmonary function studies [154].

Urticaria

An anecdote of benefit for a patient with chronic urticaria has been detailed in which the rash disappeared on pharmacological doses of the drug [155].

Alzheimer's disease

As indicated above, there is growing evidence of mefenamic acid being capable of providing neuroprotection. Most of the latter evidence has been obtained *in vitro*, but recent studies of protection in animal models are enticing [37]. The latter study was able to determine that mefenamic acid could improve cognitive impairment in a rat model of Alzheimer's disease. Along this line, human use of NSAIDs for the treatment of Alzheimer's has received increasing attention, but a contemporary cumulative analysis of the latter could not confirm a benefit for clinical use at this time [156].

Adverse effects

General

The frequency of side effects when using mefenamic acid is considerably detailed. The understanding of the latter is complicated, however, by the diversity in reporting over several decades. Reports of toxicity have often been focused on major side effects, in which the frequencies would seem rather low. On the contrary, others have reported all side effects including minor or transient ones, thereby resulting in a seemingly high frequency. A retrospective review of side effects cannot reliably distinguish studies that may have been biased by industry support or industry-recommended schemata. Some studies have used directed side-effect categories, in contrast to others in which patients record any pattern of adverse effect.

Most studies reporting side effects have involved patients who ingested multiple doses. By far, the patients in these reports have ingested daily doses of 500 mg three times per day. Generalizing, there is an apparent increase in reported side effects to parallel an increased daily dose [157]. As well, prolonged use is generally associated with more side effects. Given the variation of illnesses for which mefenamic acid may be used, the baseline frequency

of comorbidities in some patient groups may be high [82]. It is important, therefore, to appreciate such baseline symptoms in order to better understand what may truly be attributable to mefenamic acid. The placebo effect on symptoms has been well recognized, even in comparative studies that include mefenamic acid. It is indisputable that clinical doses of mefenamic acid are associated with a higher frequency of side effects compared with placebo.

The discontinuation frequency for mefenamic acid in various studies has ranged from 0 to 17.9%. Some of these analyses have included long-term use. Table 1 outlines the frequency profile for different side effects. The overall side-effect frequency for individual publications (i.e., whether of minor or major complaints) has varied from 0 to 58.3%. For a tally of 37 such reports which include 1854 patients, the total frequency has been 15.1%. Few studies have commented on laboratory indices of blood and chemistry, and these do not report differences between mefenamic acid and placebo.

In comparative evaluations, mefenamic acid has proven to cause a similar side-effect frequency to paracetamol, zomepirac, fenoprofen, ibuprofen, ASA, dextropropoxyphene/paracetamol, diflunisal, diclofenac, ketoprofen, naproxen, piroxicam and placebo. It is remarkable that, among such reports, several have found the adverse reaction rate to be no different than placebo [83,84,96,119,120,130,134–136]. One report found a greater frequency of side effects for mefenamic acid over placebo for the category of diarrhea alone [59]. Another report found a greater frequency for mefenamic acid over ASA [158].

Allergy to mefenamic acid can cross over to allergies with other NSAIDs (including ASA), and indeed may induce allergic bronchoconstriction [159]. It is not surprising, therefore, that the induction of tolerance to ASA can facilitate tolerance to mefenamic acid [160]. There are nevertheless patients who are selectively allergic to mefenamic acid or other NSAIDs [161], and so judicious use in the ASA-allergic patient must weigh benefit and risk. Anaphylaxis to mefenamic acid has been cited [162,163]. With the diversity of toxic events that have been attributed to mefenamic acid, a unifying theme of mechanism(s) for such toxicity has not been established, but it has been suggested that the pro-oxidant effects of the drug might have a role in idiosyncratic toxicity [164]. The genetic bases for susceptibility to such toxic effects also are yet to be defined. With anecdotes of toxicity among the elderly, some raised hesitation with the use of this agent among the elderly population, especially citing long-term use as a potential problem [165]. The latter could be said, however, of most, if not all, NSAIDs.

Table 1. The spectrum of adverse reactions reported in clinical studies of mefenamic acid use.

Side effect	Incidence (%)
Epigastric and abdominal pain	0–35
Headache	0–22.2
Nausea and anorexia	0–20
Fatigue	0–18.2
Diarrhea	0–16.7
Skin rash	0–12.5
Emesis	0–11.7
Dizziness and vertigo	0–9.1
Bloating	0–6.3
Lower limb edema	0–5.6
Fluid retention	0–5
Drowsiness	0–4.7
Constipation	0–4.5
Depression	0–4.4
Blurred vision	0–4.2
Oral canker	0–2.5
Diaphoresis	0–2.4
Nervousness	0–2.1
Insomnia	0–2.1
Fever	0–1.4
Dry mouth	0–1.4
Tinnitus	0–1.3
Flatulence	0–0.9
Dry eyes	0–0.9
Nightmares	0–0.9

Specific

Skin

Generalized allergic reactions are similar to those that may be suffered with other NSAIDs (Table 1). Particularly, interesting variations on this theme include Stevens–Johnson syndrome, bullous pemphigoid, toxic epidermolysis, linear IgA bullous dermatosis and fixed-drug (focal or multifocal) eruptions [166–171]. In a study from Pakistan, in which the denominator for mefenamic use in the general population was not detailed, mefenamic acid was among the more common etiological agents of fixed-drug eruptions. An increase in the incidence of rash with the increase of dose used has been recognized [157].

Renal

Nephrotoxicity has been cited on many occasions. It is postulated that interference on the regulation of renal blood flow via prostaglandin-dependent mechanisms is a major factor in such toxicity. Cytotoxicity to renal medulla interstitial cells, however, has been reproduced *in vitro* [172]. In animal models, high doses of mefenamic acid can frequently lead to papillary necrosis [173], but such disease can be reduced by PGE_2 analogues. Caffeine can potentiate the toxicity in such models.

Short-term use of mefenamic acid is unlikely to lead to renal side effects [174]. Nevertheless, there are several descriptions of renal failure, including nonoliguric forms, although especially among the elderly [175,176]. Histopathology commonly reveals interstitial nephritis with mesangial proliferation [177,178]. The

latter is quickly reversible when the drug is discontinued [179]. In one report, the interstitial disease was followed by fibrosis [180]. Renal papillary necrosis has also been linked to mefenamic acid as it has for other NSAIDs [181,182]. Early studies did not find a significant change in blood urea nitrogen when different doses of mefenamic acid were used [157].

There are no studies of mefenamic acid effects on blood pressure in the long term, whether through kidney-mediated processes or others. In this regard, it is also noted that mefenamic acid overdose is not associated with acute hypertension. It remains to be determined whether this agent can be associated with increases in blood pressure, as has been suggested for other NSAIDs.

Central nervous system

The potential for mefenamic acid to act on the CNS was noted in animal model studies in which the drug caused a short-lived depressant effect at low doses and a stimulant effect in high doses [183]. Extrapyramidal symptoms have rarely been described among humans [184]. In overdose situations, muscle twitching and seizures are common [185,186]; however, anticonvulsant properties for mefenamic acid have been proposed [30]. $GABA_A$-receptor modulation, both potentiation and inhibition, with this pharmacological agent is complex [30].

Enteropathy

An association of NSAIDs with enteropathy was recognized early, and thereafter, studies of mefenamic acid-associated similar illnesses were viewed with interest since the newly developed drugs were to hold promise if such pathology was spared. Mefenamic acid can decrease gastrointestinal blood flow [187]. Consumption of mefenamic acid was associated with intestinal blood loss less than or equal to ASA in therapeutic doses [157,188,189]. Esophageal ulceration was reported anecdotally in a patient consuming the drug before bedtime [190]. Gastric erosions or ulcers were documented for both humans and animal models in a dose-dependent fashion [20,191,192]. In animal models, mefenamic acid appeared to be associated with lesser gastric pathology than ASA, indomethacin and fenoprofen [191], although one study found mefenamic acid to have a higher frequency in comparison with all other NSAIDs studied [20]. In observational studies among humans, mefenamic acid (along with ibuprofen and celecoxib) was associated with the same frequency of gastrointestinal toxicity as other NSAIDs [193]. By the 1990s, when there was an existing plethora of NSAIDs, mefenamic acid ranked intermediate among NSAIDs for gastrointestinal toxicity [194]. A study has found the gastrointestinal intolerance to be dose-dependent [157]. However, most gastrointestinal-related side effects are either epigastric or abdominal pain or diarrhea (Table 1).

Erosions can extend into the duodenum, jejunum and ileum, although the duodenal pathology was uncommon among other NSAIDs [195]. Apart from erosive enteropathy, several citations emerged of mefenamic acid-associated villous atrophy of the small bowel [196–200]. The latter could be accompanied by diarrhea, steatorrhea and weight loss, and these were readily reversible after the drug use was terminated. The potential for large bowel toxicity was also confirmed in the finding of large bowel erosions and proctocolitis [201–203]. One study reported that approximately 10% of new colitides could be associated with NSAID use (to include mefenamic acid) [204]. There is an isolated report of association with small bowel hematoma [205]. *In vitro*, mefenamic acid can be cytotoxic to intestinal cell lines [206].

Liver & pancreas

Liver and pancreatic functions are rarely affected. An episode of mefenamic acid-associated pancreatitis has been reported [105]. Minor changes in γ-glutamyl transferase have been documented among females who have long-term intermittent use [73]. Toxicity to liver *in vivo* or *in vitro* in laboratory models can be seen and is dose-dependent [207,208]. A report of cholestatic hepatitis is complicated by multiple agent use [209].

Hematological

An effect on red blood cell stability and coagulation has been recognized, although this was not established in early studies [157]. Most commonly cited among these is the potential for drug-induced hemolytic anemia. The latter is largely antibody-mediated (Coomb's positive), although Coomb's-negative hemolytic anemia has been cited as well [167,210–212]. Among NSAIDs, mefenamic acid is among the most common to cause hemolytic anemia. Mefenamic acid can increase osmotic fragility of red blood cells *in vitro* [213]. The pharmacological agent can enhance the anticoagulant effect of warfarin whether or not the prothrombin time is prolonged [214]. The latter is in contrast to early studies, which found no significant change in the prothrombin time when warfarin was coingested [157]. One study proposed an association of mefenamic acid use and venous thromboembolism [215].

An effect of mefenamic acid on myeloid cells has been particularly cited in the form of neutropenia [216]. In one episode, bone marrow examinations revealed an arrest of myeloid cell maturation that could be reversed by granulocyte-stimulating factor [217]. *In vitro* studies show a potential effect on several neutrophil functions [218]. Mefenamic acid does not appear to have an effect on uric acid levels [219].

Other side effects

Anecdotes of mefenamic acid toxicity have included reversible glaucoma, induction of both IgA autoantibody and anti-DNA antibody, pseudoporphyria and phototoxicity, delay in menses and cleft palate (mice) [220–224].

Overdose

The frequency of mefenamic acid use in episodes of overdose or other intentional or nonintentional overuse evidently followed the drug's popularity and prescription frequency. In Scotland over the interval 1971–1985, mefenamic acid was a common agent for overdose, albeit less often than ASA and acetaminophen [225]. The latter occurred in a context where approximately 50% of all misuse drugs were NSAIDs. In a smaller study from Edinburgh (Scotland, UK), approximately 70% of analgesic overdoses were attributed to mefenamic acid [226]. During 1980–1986,

the National Poison Information Service based in London, UK, found that the pharmacological agent was the most common NSAID reported in overdoses [227]. The majority of these patients were young females less than 30 years of age. During the 1990s, Saudi Arabia physicians reported that mefenamic acid was the single most common agent used in overdose [228].

Among humans, ingestions of up to 50 g have occurred with associated toxicity and eventual resolution [175,229,230]. Human blood levels during toxicity of overdose have been determined in the range of 40–250 mg/l [175,229,231]. An episode of intravenous abuse has also been reported [232].

Episodes of overdose have clearly defined mefenamic acid as a neurotoxin with seizures, drowsiness, coma, muscle fasciculation and reduced consciousness. It has been purported that mefenamic acid causes more CNS manifestations with overdose than most other NSAIDs [233]. Other side effects during overdose have included abdominal pain, emesis, bloody diarrhea, renal failure, cardiac arrest, respiratory arrest and prolonged prothrombin time.

Seizures generally respond to supportive care and diazepam. Hemodialysis does not clear mefenamic acid [234]. Oral absorption can be reduced by up to 30–40% by charcoal, and it is recommended that 5 g of charcoal be given for each 1 g of mefenamic acid ingested [235]. Lavage may be attempted in the early stages of overdose. In many instances, purely supportive care may suffice.

In animal models (rats and mice), the median lethal dose was reported as approximately 400 mg/kg/day with a variable toxicity interval among subject animals [1,192]. Oral doses are less toxic due to absorption limitations, and up to 1400 mg/kg/day have been given. Among dogs and monkeys, oral doses of 200–600 mg/kg/day evoke considerable toxicity in the short term [192].

Abuse potential

Mefenamic acid does not attract individuals to use the drug for recreational purposes, and it does not have mood-enhancing properties, nor is it combined with other agents for these purposes. In regards to drug abuse, it has been added to some preparations as an adulterant, thus giving a pharmacological effect that might otherwise be attributed to the coingestant.

Drug–drug interactions

Mefenamic acid can displace valproic acid from albumin-binding sites [236]. It may adversely interact with cyclosporine or lithium to impair renal function [237–239]. A coingestion with diclofenac was described in a child with CNS toxicity [240]. Coingestion with iodine was also associated with toxicity [241].

Conclusion

Mefenamic acid has established itself as a valuable pharmacological agent in pain management and focused gynecological maladies. Several authors have raised concern with toxicity of the gastrointestinal tract. Comparative prospective studies, however, have largely determined that the frequency of such toxicity is equivalent to other NSAIDs. Likewise, concern particularly for use among the elderly, especially long-term usage, has been flagged, but such toxicity is also shared for most other NSAIDs. There is ample reason to believe that mefenamic acid can continue to be used in several clinical settings and remain cost-effective and active.

The basic sciences have opened a window of opportunity for mefenamic acid to be used alone or perhaps in conjunction with other drugs for some new indications. For example, the effect of mefenamic acid to modulate chronic progressive brain pathology is deserving of further investigations. Cellular mechanisms of action could be particularly exploited to effect cellular, and then macroscopic, change in many innovative applications.

Toxicity profiles suggest that mefenamic acid should be used in the range of 1–1.5 g daily in divided doses. While most publications have assessed the agent when used at 1.5 g daily, lesser daily doses may suffice and yet be accompanied by more acceptable and less toxicity. Long-term daily use of mefenamic acid, as for other NSAIDs, should be judiciously monitored.

Expert commentary

In an era of escalating healthcare costs, a re-evaluation of existing but perhaps equally effective pharmacological agents is imperative. Not only do we return to using medicines that are cost effective, but we may yet realize the further potential of these agents. Mefenamic acid is a good example of this.

Narcotic use and abuse is a worldwide concern, and the creative use of NSAIDs in focused settings may be prudent especially in the general area of pain control. Concepts of alternating pain medications, simultaneous pharmacological agent use and frank replacement are all potential considerations for mefenamic acid use in this context.

Given the vast array of biochemical actions for mefenamic acid, there may yet remain several other avenues for use at both seemingly pharmacological and subtherapeutic doses. In addition to pain management, innovation in the areas of neuroprotection and cardioprotection is yet to be fully explored. As mefenamic acid-associated toxicity is often dose-related, more studies of 1 g daily dosing appear to be warranted. Although NSAIDs are often thought to have cross-allergies, there may be exceptions for several patients, thus inviting a trial of mefenamic acid.

Five-year view

Mefenamic acid will continue to maintain a role in the pharmacology of healthcare, and its use will continue worldwide. Although mainly used for anti-inflammatory and pain directives, there is considerable opportunity for expanding the role of this and other NSAIDs. Given the availability of mefenamic acid in generic form, potential cost savings may be attractive to public health providers. It would be sensible to re-examine this agent's use for efficacy but with the added rationale of cost saving. Chronic pain management is a key potential focus for expanded use in an era where narcotic misuse is abundant. New methods of drug delivery are likely to attract attention.

Basic science research needs to continue, especially with niche foci. For example, the potential for modulating central nervous system pathologies deserves further attention. Alongside the

potential for expanding mefenamic acid use, it will be incumbent upon those researchers to further the appreciation of long-term applications.

Acknowledgements

This paper is dedicated to the memory of Francis Cimolai. The author would like to thank Debra Cimolai for support in the preparation of the manuscript.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Mefenamic acid has been extensively investigated in the basic sciences and has a great diversity of biochemical and physiological activities.
- Mefenamic acid is generally equivalent to most other NSAIDs for pain control and anti-inflammatory effect.
- The typical total daily dose for human use is 750–1500 mg.
- There was historically focused use for various gynecological disorders but there is potential value for many other pain syndromes.
- Key foci for toxicity include skin, kidney, intestinal tract and blood, but generally the frequency of mefenamic acid adverse effects is similar to those of other NSAIDs.
- Mefenamic acid does not attract recreational use, but there are a considerable number of publications in regards to use in overdose.

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- **Management of NSAID toxicity.**

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