

Ibuprofen : a review of its pharmacology, efficacy and safety in respiratory and neurological disease

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Abstract

Ibudilast is a relatively non-selective phosphodiesterase inhibitor which has been marketed for almost 20 years in Japan for treating asthma. More recently it has been found to have anti-inflammatory activity in both the peripheral immune system and in the central nervous system via glial cell attenuation. This CNS-directed anti-inflammatory activity is of potential use in the treatment of multiple sclerosis, neuropathic pain, and in the improved efficacy and safety of opioids by decreasing opioid tolerance, withdrawal and reinforcement. Its suitable pharmacokinetics and generally good tolerability make it a promising potential treatment for these conditions.

Keywords (in alphabetical order)

glia

ibudilast

multiple sclerosis

neuropathic pain

priming

1. Introduction

Ibutilast has been marketed for almost 2 decades in Japan for the treatment of asthma and post-stroke dizziness, presumably because of the bronchodilator and vasodilator effects of phosphodiesterase (PDE) inhibition attributed to the drug. More recently, additional anti-inflammatory actions of ibutilast have been discovered. These shed light not only into its claimed action in asthma, but suggest therapeutic utility in other respiratory diseases as well as a range of neurological diseases including multiple sclerosis, neuropathic pain, and opioid addiction. This review summarises the pharmacology, efficacy and safety of ibutilast in these respiratory and neurological conditions.

2. Market overview

2.1 Asthma and COPD

The mainstays of pharmacotherapy for asthma are inhaled corticosteroids, short- and/or long-acting inhaled beta₂ agonists, and oral leukotriene inhibitors. Non-selective PDE inhibitors such as theophylline or ibutilast have long been utilized, but are no longer predominant. In comparison to theophylline, ibutilast is a more potent PDE-3 and -4 inhibitor and has a better clinical pharmacokinetic and side effect profile. Accordingly, it retains greater per capita use in Japan where it is approved than does theophylline in the U.S.A. A respiratory disease which is receiving increasing attention for unmet need is chronic obstructive pulmonary disease (COPD). PDE 3/4 inhibitors with clearly demonstrated anti-inflammatory activity represent key therapeutic candidates for respiratory indications like COPD [1]. What has limited the development of most of those drug leads is gastrointestinal side effects. As ibutilast has an appropriate PDE-inhibitor and anti-inflammatory profile with acceptable gastrointestinal tolerability at efficacious doses, it may represent a competitive candidate for consideration in COPD pharmacotherapy.

2.2 Multiple sclerosis (MS)

Current licensed therapies for MS include beta-interferon and glatiramer. These treatments are given by injection and especially with beta-interferon are associated with a high rate of adverse effects. Acute disease may be treated with corticosteroids. Efficacy is modest with all treatments. Hence, there is a high unmet medical need for an orally active well tolerated efficacious treatment to reduce disease progression. The majority of late-stage drugs in development for multiple sclerosis target peripheral immune processes in early disease. As reviewed in [2], dysregulation of glia has been linked to multiple sclerosis pathology and inherited neurodegenerative diseases. Accordingly, a glial attenuator such as ibudilast may be a useful treatment.

2.3 Chronic neuropathic pain

Despite some recent advances in drug treatment for chronic neuropathic pain, it remains challenging to treat. The current repertoire of drugs, mainly tricyclic antidepressants, anticonvulsants and opioids is inadequate due to limited efficacy and/or unsatisfactory tolerability. An evolving drug target with substantial preclinical validation is glial attenuation [3,4]. Two such drug candidates in clinical development are propentofylline (SLC022) and ibudilast (AV411 or MN166). A major potential advantage of targeting glia is the possibility of therapeutic benefit with a reduced CNS adverse effect profile.

2.4 Opioid dependence

The pharmacological management of opioid addiction is an adjunct to psychotherapy. Pharmacotherapies include opioid substitution with methadone and buprenorphine, rapid detoxification assisted with sympatholytics such as clonidine and antagonist therapy with naltrexone. Non-opioid treatments which reduce tolerance and/or attenuate withdrawal would aid in the outpatient management, especially for detoxification. Moreover, lessening abuse-related reward, and hence opioid abuse liability, may limit addiction development or reduce relapse phenomena. As described below, glial activation may contribute to all these phenomena.

3. Pharmacology

3.1 Basic Pharmacology

Ibudilast is a pyrazolo-pyridine small molecule (MW 230 : see Figure 1) which is a relatively non-selective phosphodiesterase (PDE) inhibitor. It inhibits human PDEs 3,4,10 and 11 with IC_{50} s ranging from approximately 1-10 μ M [5,6]. Given the modest but proven efficacy of PDE4 inhibitors in asthma, there is rationale for the use of this compound in asthma. In guinea pigs, ibudilast 1-4 mg/kg iv attenuated ovalbumin challenge and leukotriene D4-induced airway constriction [7].

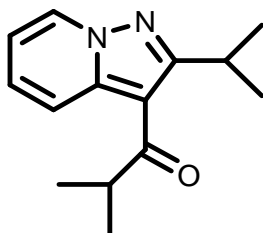


Figure 1. Chemical Structure of ibudilast

3.2 *In vitro* peripheral immune regulation

Ibudilast has been found to have a significant anti-inflammatory and immunomodulatory actions. Ibudilast was originally identified as an attenuator of leukotriene release [8] and TNF- α or IFN- γ production from peripheral white blood cells of ibudilast-treated patients [9], histamine release from mast cells [10] thromboxane generation [11] and integrin expression by eosinophils [12], some of which were attributed to its PDE actions [11] and all beneficial for the first indication as an anti-asthmatic [13].

3.3 *In vitro* central nervous system immunology

More recently, ibudilast has been recognized for its ability to also modify innate immunity in the central nervous system. Ibudilast has anti-inflammatory actions on several non-neuronal cell types within the CNS. *In vitro*, ibudilast is capable of attenuating kainite-induced

oligodendrocyte cell toxicity [14,15] and astrocyte apoptosis induced in an *in vitro* model of reperfusion [16]. Microglial activation is dose dependently reduced by ibudilast [17,18,19] with reductions in lipopolysaccharide induced nitric oxide, reactive oxygen species, interleukin-1 β , interleukin-6, and TNF- α production and enhanced production of the anti-inflammatory cytokine, interleukin-10 [17]. Microglial production of the chemokine MCP-1 is also reduced [18]. Proinflammatory interactions between peripheral and central immune cells are also ameliorated by ibudilast, with reductions in myelin basic protein induced IL-12, IFN- γ release and T cell proliferation [20]. Most recently, researchers have discovered that ibudilast is a potent inhibitor of the activity of macrophage migration inhibitory factor (MIF) – a long-recognized and well-studied proinflammatory cytokine [21]. As MIF has been linked to both peripheral and central inflammatory conditions – including glial activation – such target action may be a unifying component of ibudilast's broad actions.

3.4 *In vivo* action: general

As this wealth of *in vitro* data would suggest, when used *in vivo*, ibudilast has beneficial actions in inflammation in the CNS where glial activation contributes to the pathologies. For example, ibudilast attenuates rat experimental autoimmune encephalomyelitis [20], reduces white matter damage after chronic cerebral hypoperfusion [22], and decreases the number of TNF- α labeled cells in a genetic model of Krabbe's disease [23]. The rationale for the use of ibudilast in post-stroke dizziness is not clear. PDE inhibitors produce some vasodilating activity and the assumption that post-stroke dizziness is due to ongoing ischaemia may be the rationale for the use of the drug in this condition. Additionally, astrocyte involvement in neovascular regulation [24] might confer a glial-based mechanism for ibudilast's cerebrovascular benefit.

3.5 *In vivo* action: preclinical neuropathic pain

Until relatively recently, conceptualization of neuropathic pain had been exclusively neuronally-based with most drugs in development being for neuronal targets. These targets have been revised significantly in light of the profound role glial activation has in creating and

sustaining enhanced maladaptive pain states [25]. Several mechanisms of glial activation resulting in neuropathic pain have been established, including the most recent addition of a role for the innate immune receptor Toll Like Receptor 4 (TLR4) in creating and maintaining exaggerated pain states activated by endogenous danger signals elevated following nerve damage. Hence, glially targeted pharmacotherapies that attenuate glial pro-inflammation are under development for neuropathic pain. For example, ibudilast and its glial-active analogs have demonstrated significant pain relief in several animal models of neuropathic pain including chronic constriction injury (CCI), Chung (L5/L6 nerve ligation), and paclitaxel-induced allodynia [18,26]. Moreover, ibudilast also showed efficacy in a rat model of mixed peripheral and central pain. Combined spinal cord and nerve root injury (unilateral T13 & L1 dorsal nerve root avulsion) leads to glial activation and bilateral mechanical allodynia. Ibudilast was able to reverse mechanical allodynia to nearly pre-injury levels [27]. These animal pharmacology results suggest that onset of efficacy is achieved with plasma ibudilast exposures which are clinically achievable. Additionally, immunohistochemistry of glial markers indicate significantly reduced glial activation in the spinal cord concordant with relief of allodynia [27].

3.6 In vivo action: opioid analgesia, reward and withdrawal

General immune involvement in opioid action was first investigated nearly 3 decades ago [28] in studies that found several global immunosuppressive drugs attenuated morphine withdrawal in rats. Importantly, these studies were conducted prior to an appreciation of the importance of glia, and it is probable that the immunosuppressants would have suppressed glial activation, thereby in retrospect unknowingly implicating glia in opioid action. The broader implications of this research was not fully realized until 2001 when Song and Zhao [29] demonstrated opioid-induced glial activation opposed chronic opioid analgesia, thereby demonstrating opioid-induced proinflammatory glial activation could in turn impact opioid pharmacodynamics. The breadth of opioid actions that are impacted by opioid-induced glial activation is impressive, with opposition of acute and chronic opioid analgesia, contribution in the development of analgesic tolerance, opioid induced hyperalgesia and allodynia,

withdrawal allodynia, opioid dependence, opioid reward and opioid induced respiratory depression [30,31,32,33]. Ibudilast is efficacious in several rat models of these actions. Firstly, ibudilast robustly potentiates both acute analgesia to morphine and oxycodone, assessed by a modified Hargreaves method [32]. Drugs of abuse, such as morphine, cause increased dopamine levels in the nucleus accumbens, and this is thought to mediate the internal reward (reinforcement) associated with such drugs [34]. Rats dependent on morphine showed an elevation in dopamine in the nucleus accumbens immediately following administration of morphine, as determined by microdialysis. Co-administration of ibudilast with morphine to dependent rats reduced the dopamine increase [35]. Ibudilast was also investigated in a standard rat model of morphine withdrawal precipitated by naloxone. Rats were administered increasing doses of morphine to establish dependence over a five day period, prior to naloxone administration. Concomitant treatment with ibudilast, initiated following the onset of morphine dosing, significantly reduced withdrawal behaviors in morphine-dependent rats across the 60 min observation period [32]. In a similar fashion to the reduction in withdrawal behaviors and weight loss, a corresponding reduction in glial activation markers was also observed in several brain regions following morphine + ibudilast treatment compared to morphine + vehicle treatment. On the basis of these and other studies, ibudilast is being assessed for opioid withdrawal utility in heroin-dependent patients at Columbia University/New York State Psychiatric Institute.

4. Pharmacokinetics and metabolism

4.1 Preclinical

Despite ibudilast's long-standing use in Japan, limited pharmacokinetic and metabolism characterization has been published in animals or humans. Some information related to ¹⁴C-ibudilast absorption, distribution, and excretion after oral administration in rats, dogs, and monkeys published more than 20 years ago provided some information but was hampered by the lack of discrimination of parent vs metabolites [36]. Radioactivity distributed well to peripheral and central tissues and was excreted primarily in urine, but also in feces. Plasma protein binding of total radioactivity in orally-dosed rats was approximately 98%. In terms of

metabolism, a study published in 1990 [37] utilizing hepatic microsomes from rats and humans showed that ibudilast mainly undergoes hydroxylation at the side chains and on the pyridine ring, but the particular enzymes were not identified. As a component of Avigen's development efforts, ibudilast pharmacokinetics have been extensively profiled in preclinical and clinical studies [38,,39]. Sensitive LC-MS/MS analytics were developed and validated for analysis of ibudilast and primary metabolite(s) in human and animal plasma and urine. It has been determined that oral exposures adjusted to administered dose are higher in rats and humans than other species including dogs and monkeys and yet plasma exposure appear proportional to dose across species. Metabolism has been studied extensively and metabolite profiles are similar across species. As implicated in the early Japanese studies, plasma protein binding of ibudilast in most species is $\geq 95\%$. Moreover, ibudilast is metabolized by numerous cytochrome P450 isozymes, with the primary metabolite in humans (as well as in animals) being a 6,7-dihydrodiol metabolite. Ibudilast is not predicted to be a clinically-relevant inhibitor or inducer of CYP enzymes *in vivo* and, thus, clinically relevant drug-drug interactions are not anticipated.

4.2 Clinical pharmacokinetics

Recent clinical pharmacology studies have shed additional light on human pharmacokinetics (Avigen trials 016 and 026). The pharmacokinetics of ibudilast were previously examined after a single 30 mg dose and after multiple doses of 30 mg twice daily for 14 days in nine healthy men and nine healthy Caucasian women [39]. A commercial modified release formulation (Pinatos) was used in this and studies described below. Peak plasma concentrations after the single dose were 32 ng/ml reached at a median of five hours. The apparent elimination half life was 19 hours. Steady-state was reached by day two. Negligible drug was eliminated in the urine. These results corroborate well with earlier studies in Japanese at lower doses although dose-adjusted exposure in Japanese was slightly higher.

Single-dose pharmacokinetics were linear over a higher doses range from 30-100 mg in healthy male and female volunteers. Absorption was non-significantly increased approximately 10% with a high-fat meal. Apparent clearance when fasted was approximately 650 ml/min. In a two-week repeat dose study comparing the tolerability and pharmacokinetics of ibudilast 20-50 mg bid in 12 healthy subjects and 12 diabetics, it was generally well tolerated in both populations albeit with somewhat increased GI side effects in the diabetic subjects. No significant differences were found in ibudilast pharmacokinetics between the groups and were, furthermore, comparable with other studies [39]. However, the diabetics had slightly lower circulating levels of the 6,7-dihydrodiol metabolite and corresponding slightly higher plasma ibudilast levels. Ibudilast pharmacokinetics have been generally dose-proportional in single administration or repeat dose trials. Interestingly, while plasma ibudilast levels in multi-day repeat dosing studies in rats display significant diminution within 1-2 weeks, steady-state drug levels remain stable in humans for at least two weeks of repeat dosing [38,39].

Ibudilast is negligibly excreted in urine as unchanged drug. A major metabolite, 6, 7 – dihydrodiol ibudilast was detected in plasma, at concentrations averaging 30-40% of the parent. Low levels of monohydroxylated metabolite and glucuronides of the mono and dihydro metabolites were detected in urine.

5. Clinical efficacy

5.1 Asthma

As mentioned above, trials of high quality supporting the use of ibudilast in the licensed conditions of asthma and post-stroke dizziness are generally lacking.

Ibudilast is generally used for the indication of asthma at doses of 10 mg two or three times daily. However there are few publications showing efficacy in asthma of adequately powered and blinded design. In what appears to be an open-label study with an untreated control group, histamine bronchial challenge sensitivity and symptoms were reduced by ibudilast 20 mg twice-daily given to 13 asthmatic patients and these effects were superior to

those with cromolyn [13]. Additionally, another open-label trial in 86 asthma patients and ibudilast dosing ranging from 10 to 40 mg/day yielded clinical benefit at all dose levels and without clear differences at mid (20 mg/d) or high (40 mg/day) dose levels [40].

5.2 Post-stroke dizziness

In a controlled single dose of study in 41 patients with non-insulin-dependent diabetes, 10 mg ibudilast increased the diameter of and flow through the dorsalis pedis artery [41]. In an open-label trial, eleven patients with chronic cerebral vascular disease complaining of dizziness or depression were treated with ibudilast 30 mg / day. All patients reported resolution of dizziness at six months and of the six patients with depression all experienced significant improvement. Cerebral blood flow was increased in the right frontal and occipital visual cortex areas. However given the non-controlled nature of this study little value can be placed on it [42].

5.3 Neuropathic pain

A safety, tolerability and preliminary efficacy study of ibudilast was conducted in patients with painful diabetic neuropathy or complex regional pain syndrome. The study was of placebo-controlled design in which patients received single doses of between 10-40mg and 14 days at 20 mg bid (n=4); 20 mg tid (n=4) or 30 mg escalated after two days to 40 mg bid (n=16) for two weeks total. Treatment with analgesics and other pain modifying drugs was continued unchanged. Nausea, diarrhoea and fatigue, which tended to accommodate in the second week, were more commonly reported in patients on active treatment whereas more patients reported headache on placebo [43].

Overall, patients in both placebo and active treated groups showed a pain scale improvement by a median of 2 points on a 10 unit scale. However there was a non-significant trend ($p = 0.07$ Chi Sq test) for patients with higher exposure ($AUC > 1000$ ng/ml*hr) to perform better: 6/10 were responders (defined as ≥ 1 cm change in visual analog scale pain score from day 20 to day 8 (the first day of dosing) compared to 2/8 with

AUC lower than 1000 ng/ml*hr. This trend was present across all 3 pertinent PK parameters

– i.e. C_{max}, C_{min}, AUC₀₋₂₄ as shown below:

Plasma Parameter		VAS 'Responder' %
AUC0-24h	> 1000 ng*hr/mL	60%
	< 1000 ng*hr/mL	25%
Cmax	> 60 ng/mL	64%
	< 60 ng/mL	14%
Cmin	> 27 ng/mL	55%
	< 27 ng/mL	29%

As patients were allowed to take analgesics as required, changes in opioid consumption (as average daily dose of morphine equivalents) was examined as a possible efficacy measure. When the end-of-study morphine equivalent use was calculated and compared to the average first-week dosing daily average, a non-significant trend for reduced opioid usage was observed. Amongst opioid users, the placebo group showed a median morphine equivalent use increase of approximately 18 mg, whereas the 40 mg BID treatment group exhibited a reduction of approximately 7 mg morphine equivalents.

Hence, this study showed some indicators of a potential Ibudilast effect in patients with neuropathic pain as evidenced by a non-significant correlation between clinical pain response and drug exposure and a weak trend for opioid sparing. However the data are only suggestive and need confirmation in a larger study at high doses.

5.4 Multiple sclerosis

MediciNova has reported a 2 year trial of double blind placebo-controlled ibudilast 10-20 mg tid in 297 patients with multiple sclerosis (MS). The study has not been published but data have been presented at a scientific meeting (European Neurological Society 2008 and company press releases). The primary endpoint of a reduction in cumulative new lesion

count was not met. However the highest dose, at both years 1 and 2, produced a significant reduction in percent brain volume loss, time to first relapse, disability progression and probability of new lesions evolving to persistent “black holes”. These data suggest that ibudilast has neuroprotectant and anti-inflammatory effects in the CNS as a dose of 60 mg/day. Although pain can be a symptom in MS, no assessment was reported about effects of study drug on pain.

6. Clinical safety and tolerability

Unlike more selective PDE-4 inhibitors which are accompanied by high rates of nausea at therapeutic doses, ibudilast appears to be well tolerated at the doses used in asthma and higher.

The package insert for modified-release ibudilast, Ketas, lists the following adverse effects at frequency between 0.1-5% of patients : gastrointestinal (anorexia, nausea, vomiting abdominal pain, dyspepsia); CNS (dizziness, headache); rash and elevated liver function tests. Less frequent were itch, tremor, insomnia, sleepiness, apathy, diarrhoea, palpitation, hot flushes, bilirubin elevation, and thrombocytopenia.

In completed studies performed by Avigen to date (ibudilast n=101; placebo n=35) the primary adverse effect reported more frequently on active drug was GI-related, particularly nausea, diarrhea, and dyspepsia. Given the PDE inhibiting action, GI upset being among the commonest adverse effects is to be expected. However, most of these adverse effects are of minor clinical significance. In the tolerability study in healthy subjects and diabetics mentioned above, at doses of up to 50 mg bd with peak plasma ibudilast concentrations approximating 120 ng/ml, the rate of gastrointestinal (GI) adverse events, including dyspepsia and diarrhea, were more commonly reported by subjects with diabetes receiving ibudilast than placebo and yet were not reported by healthy participants in that study. Most of the GI adverse events were assessed to be possibly or probably related to study

medication. All but one of the diabetic subjects were taking metformin as a concomitant medication throughout the study which may have contributed as such GI AE are recognized symptoms with metformin.

In the 2 year trial of ibudilast 10-20 mg tid, MediciNova has reported that GI adverse effects were reported more frequently with ibudilast(30 mg / day: 11.6%; 60 mg / day: 15.2%) compared to placebo (7.8%) but that tolerance to these developed rapidly within 2-4 days. It was stated that depression (which has been associated with β -interferon, a standard treatment for MS) occurred more frequently in year 2 at 60 mg / day ibudilast than with placebo but details were not provided and ibudilast has separately been reported to benefit depression in a small open-label study in patients with cerebrovascular disease [42].

These data show that the maximum tolerated dose of ibudilast in humans has not yet been demonstrated and that clinical tolerability appears good.

7. Regulatory status

Ibudilast is marketed as Ketas or Pinatos in Japan for asthma and post-stroke dizziness. Also for the for the treatment of ocular allergies in a 0.01% ophthalmic solution as Ketas[®] drops (Senju Pharmaceutical Co., Japan; Handok Pharma, South Korea) and Eyevinal[®] (Banyu Pharmaceutical Co., Japan). In the US IND's are open for neuropathic pain and opioid withdrawal. The trials in Australia were performed under the Clinical Trial Notification scheme.

8. Expert opinion.

Ibudilast has a range of immunomodulatory and anti-inflammatory activity in both circulating white cells and central nervous system glial cells. There are insufficient published data from adequately powered and blinded efficacy studies in asthma to conclude that it is efficacious for this licensed indication. However if it is effective, it is likely that is a significant

component of its efficacy is through peripheral immunomodulatory and anti-inflammatory action. This also might explain why the adverse effect profile of ibudilast appears to produce less nausea than other anti-asthmatic PDE-4 inhibitors, as its efficacy is not dependent on this mechanism. In terms of other potential respiratory indications, utility in COPD is feasible, but must be specifically developed.

The potential clinical targets for ibudilast in neurological disease, including MS, neuropathic pain and addiction comprise a large populations of patients with chronic illness where current treatment is often unsatisfactory, due to poor tolerability and sub-optimal efficacy. From the available data, it appears that ibudilast is well-tolerated, and a maximum tolerated dose has not yet been clearly established. For neuropathic pain and addiction, almost all available treatments are primarily directed to neuronal targets which contributes to the poor tolerability which may limit efficacy by restricting the available dosage range. Ibudilast potentially offers a notably different treatment approach to these illnesses. There is also the possibility of the drug being disease-modifying unlike many of the current treatments, which are simply suppressive of symptoms. However, all these potential benefits are still currently theoretical, as published studies in peer-reviewed journals supporting efficacy in any neurological condition are lacking. Tolerability is generally good, with dose-related nausea the most frequently reported adverse effect, and may be consistent with PDE-inhibition. However, the full profile of ibudilast safety at targeted doses for CNS indications awaits further clinical development.

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