

# The Pruritus of Cholestasis

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The generalized pruritus, which commonly complicates cholestasis, may limit normal activities and cause sleep deprivation. Its pathogenesis is unknown and, consequently, conventional therapies for the pruritus of cholestasis lack a sound scientific basis.

## PATHOGENESIS

Although the pathophysiological changes responsible for mediating the pruritus of cholestasis may be present in all cholestatic patients, there may be interindividual differences that influence its perception. This concept is suggested by the lack of correlation between the severity of cholestasis and the apparent intensity with which pruritus is perceived by cholestatic patients, and by the lack of this symptom in some patients with cholestasis. A spontaneous decrease in the intensity of pruritus does not necessarily imply a decrease in the severity of cholestasis and/or improvement of hepatocellular function. In some patients with chronic cholestatic liver disease, itching seems to subside spontaneously as cholestasis persists and hepatocellular failure supervenes.<sup>1</sup> This clinical impression suggests that one or more substances that contribute directly or indirectly to the pruritus, are synthesised in the liver.

### *Putative Peripherally Acting Pruritogens*

For decades it has been assumed that the pruritus of cholestasis arises as a consequence of interactions between nerve endings in the skin and one or more substances that accumulate systemically as a consequence of impaired secretion of bile. Hypotheses of pathogenesis have often been based on correlations between subjective assessments of pruritus and levels of specific substances in plasma. In this context, levels of substances in interstitial fluid of the skin may be more relevant than corresponding levels in plasma.<sup>2</sup> However, to implicate a specific substance in a peripheral pathogenic mechanism, it is necessary to show that the substance induces neurophysiological changes that mediate pruritus. This requirement has not been met for most putative peripheral pruritogens (e.g., bile acids).<sup>3</sup> The assumption that the primary event in the initiation of pruritus in cholestatic patients is peripheral within the skin may be true, but currently, this assumption is not supported by convincing data.

### *The Concept of Pruritus of Central Origin*

As a peripheral origin of the pruritus of cholestasis is currently uncertain, it is necessary to consider whether

central mechanisms may be implicated. That pruritus can arise in the brain is illustrated by the association of pruritus with certain neurological and psychiatric diseases in the absence of any skin lesion. However, pruritus of central origin may arise as a consequence of mechanisms that are independent of specific neurological or psychiatric diseases. Such mechanisms may include interactions between opioid agonist ligands and opioid receptors.<sup>4,5</sup>

**The Opioid System.** In considering whether opiate-induced pruritus might have implications for the pruritus of cholestasis, the systemic effects of opiates should be distinguished from their local effects near injection sites. The latter include histamine release, urticaria, and local pruritus, which is not reversed by the opiate antagonist naloxone and, hence, is not mediated by opioid receptors.<sup>6</sup> These local effects do not appear to have any relevance to the pruritus of cholestasis. In contrast, systemic effects of opiates include both increased central opioidergic neurotransmission (tone) and generalized pruritus.<sup>7</sup> It is the association of increased central opioidergic tone with pruritus that may have relevance to the pathogenesis of pruritus in cholestatic patients.<sup>3</sup> This concept has led to the following hypothesis being tested: "Increased opioidergic neurotransmission/neuromodulation (tone) in the central nervous system contributes to the pruritus of cholestasis."<sup>7</sup> The validity of this hypothesis depends on showing that (1) opioid receptor ligands with agonist properties mediate pruritus and scratching activity as a consequence of their interaction with central opioid receptors, (2) opioid-mediated neurotransmission/neuromodulation (tone) in the central nervous system is increased in cholestasis, and (3) opiate antagonists can ameliorate the pruritus of cholestasis.

**Opiate agonists and scratching activity of central origin.** When morphine (0.2-0.5 mg/kg) is injected intracisternally into cats, violent scratching activity is induced, which lasts for up to 90 minutes.<sup>4</sup> Furthermore, when morphine (1-10 µg) or the opioid agonist ligand (D-Ala<sup>2</sup>-N-Me-Phe<sup>4</sup>, Gly<sup>5</sup>-ol)-enkephalin, but not saline, is microinjected into the medullary dorsal horn of monkeys (*Macaca fascicularis*), dose-dependent facial scratching activity, which is reversed by naloxone, is induced.<sup>5</sup> These observations indicate that opiate agonists induce opioid receptor-mediated scratching activity of central origin.

**The status of the opioid system in cholestasis.** Five lines of evidence are consistent with opioidergic tone being increased in cholestasis. (1) The oral administration of a small dose (5 mg) of the potent opiate antagonist, nalmefene, to patients with primary biliary cirrhosis (PBC) consistently and abruptly induces an unpleasant reaction, characterized by symptoms and signs presumed to have a central origin, that may represent an opioid withdrawal-like reaction. This reaction is transient, usually subsiding spontaneously after 2 or 3 days despite continued drug administration, and does not occur when nalmefene is administered in high doses to healthy subjects.<sup>8</sup> (2) A rat model of acute cholestasis exhibits antinociception (analgesia) that is stereoselectively reversed by naloxone and, hence, is opioid receptor-mediated. In contrast, a rat model of acute hepatocellular necrosis does not exhibit naloxone-reversible antinociception.<sup>9</sup> (3) Total opioid activity in plasma is increased in a rat model of acute cholestasis,<sup>10</sup> and the concentrations of individual endogenous opioid agonists are elevated in the plasma of rats with

Abbreviations: PBC, primary biliary cirrhosis; 5-HT<sub>3</sub>, 5-hydroxytryptamine type 3.

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Received December 23, 1998; accepted February 10, 1999.

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acute cholestasis<sup>10</sup> and patients with chronic cholestasis.<sup>8</sup> (4) In a rat model of acute cholestasis mu-opioid receptors in the brain are down-regulated,<sup>11</sup> possibly as a consequence of changes in opioid receptor kinetics in response to increased availability of endogenous opioid agonists at opioid receptors. (5) Plasma extracts from patients with PBC and pruritus, but not extracts from patients with PBC without pruritus, induce naloxone-reversible facial scratching when microinjected into the medullary dorsal horn of monkeys.<sup>12</sup> Thus, plasma of patients with PBC and pruritus contains one or more substances that can induce central opioid receptor-mediated scratching activity. These five lines of evidence, taken together, strongly suggest that, in cholestasis, alterations in the opioid system occur that result in increased central opioidergic tone.<sup>7</sup>

*The effects of opiate antagonists on the pruritus of cholestasis.* Opiate antagonists ameliorate the pruritus of cholestasis<sup>13-15</sup> (see Treatment section).

**The Serotonin System.** Cholestasis-related altered opioidergic neurotransmission may lead to changes in other neurotransmitter systems, such as, the serotonin system. Such secondary changes may also contribute to the pruritus of cholestasis.

Ondansetron, a 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) serotonin receptor subtype antagonist, modulates transmission in neural pathways on which 5-HT<sub>3</sub> receptors are located and blocks opiate-induced analgesia,<sup>16</sup> a manifestation of increased opioidergic tone in cholestasis.<sup>9</sup> Furthermore, increased serotonin release leads to elevated Met-enkephalin levels in the hypothalamus, and this phenomenon is reversed by serotonin antagonists.<sup>17</sup> Thus, there appears to be a serotonergic-enkephalinergic neural connection in the hypothalamus.

Like the opioid system, the serotonin system modulates nociception (pain perception),<sup>18</sup> and by analogy with the opioid system, may also modulate the perception of pruritus, particularly if relevant connections between these two systems exist in brain areas that mediate nociception. Indeed, preliminary reports, in which a subjective endpoint was used, suggest that ondansetron may ameliorate opiate-induced pruritus.<sup>19,20</sup>

#### ASSESSMENT OF TREATMENT EFFICACY

Pruritus, which is defined as the need to scratch, is an intrinsically subjective perception that cannot be quantitated directly. Visual analogue scores of the perception of pruritus are inherently subjective and represent an inadequate and unreliable method of assessing this perception.<sup>21</sup> The design of state-of-the-art clinical trials of therapies for the pruritus of cholestasis should include an objective quantitative primary efficacy endpoint.

Scratching activity, in this context, can be defined as the behavioral consequence of this complication of cholestasis. In contrast to pruritus, scratching activity can be reliably quantitated. Data on this activity seem appropriate as a primary efficacy endpoint in clinical trials. Ideally, scratching should be continuously measured, independent of limb movements, for long periods of time (e.g., 24 hours). Instruments for doing this have been devised, validated, and applied in clinical trials.<sup>22,23</sup> These instruments involve the application of piezofilm technology to generate a scratch transducer, which is attached to a finger nail.

## TREATMENT

### *Therapies to Reverse or Ameliorate Cholestasis*

A treatment that reverses cholestasis would also be expected to reverse its consequences, such as pruritus. However, drugs that are believed to have this property, e.g., S-adenosylmethionine and ursodeoxycholic acid, have not been shown consistently to ameliorate the pruritus of cholestasis and have not been assessed specifically as treatments for this complication of cholestasis.<sup>24</sup> In contrast, the pruritus of cholestasis subsides rapidly (usually within 24 hours), if cholestasis due to mechanical obstruction of a large bile duct is relieved.

### *Therapies Relating to Putative Peripheral Pruritogens*

All trials of treatments to remove putative peripheral pruritogens or reverse their effects have used a subjective primary efficacy endpoint. Such studies have lacked a sound scientific rationale and can be classified as empiric.

The rationale for most commonly used therapies appears to be to reduce the concentrations of putative pruritogens. Examples include the anion exchange resins, cholestyramine and colestipol, and hepatic enzyme inducing drugs, such as rifampin, phenobarbital, and flumecinol.<sup>24</sup> More invasive examples include plasmapheresis, charcoal hemoperfusion, and partial external diversion of bile.<sup>24</sup> The fact that such invasive measures have been tried implies that other more conventional therapeutic approaches are not consistently efficacious. Because treatments of this type affect the metabolism of many compounds, data from trials of these treatments do not implicate any specific substance or class of substance in pathogenesis.

Antihistamines are often administered to patients with the pruritus of cholestasis. However, no skin changes consistent with histamine-mediated effects are found, and antihistamines do not appear to be efficacious.<sup>24</sup> Sedatives, such as phenobarbital, benzodiazepines, and antihistamines may have a nonspecific beneficial effect by facilitating sleep, but may impair activities that require mental concentration. Miscellaneous therapies that have been tried include ultraviolet light, lignocaine, androgens, and hydroxyethylrutosides.<sup>24</sup> None of these therapies have a clear rationale and none have been shown convincingly to be efficacious.

It continues to be standard procedure to use certain empiric therapies in practice. There is a consensus that an appreciable proportion of patients with chronic cholestatic liver diseases experience an amelioration of pruritus when treated with an anion exchange resin or rifampin, and this consensus is supported by subjective efficacy data from randomized, double-blind, controlled studies.<sup>25-27</sup> However, there is no standard generally-accepted regimen for treating the pruritus of cholestasis with conventional empiric therapies.<sup>24</sup>

### *Neurotransmitter Receptor Antagonists*

**Opiate Antagonists.** In 1979 a subcutaneous injection of naloxone, but not saline, was reported to induce a dramatic amelioration of intractable pruritus in a patient with PBC.<sup>28</sup> Subsequently, the oral administration of nalmefene to nine patients with PBC was reported to induce substantial ameliorations of pruritus, which appeared to be sustained over a 6-month period of drug administration.<sup>8</sup> These subjective

findings suggested that opiate antagonists may ameliorate the pruritus of cholestasis.

Confirmation of the efficacy of opiate antagonists in the treatment of the pruritus of cholestasis required incorporation of an appropriate objective quantitative primary efficacy endpoint into the design of clinical trials. By using a monitoring system that objectively quantitates scratching activity independent of limb movements,<sup>22</sup> scratching activity in patients with pruritus due to chronic cholestatic liver diseases was shown to be significantly less during naloxone infusions than during placebo infusions in two randomized controlled trials (Fig. 1).<sup>13,14</sup>

The available data suggest that parenterally administered naloxone may have a place in the emergency treatment of a severe exacerbation of the pruritus of cholestasis<sup>13,14</sup> and that an orally bioavailable opiate antagonist, such as nalmefene or naltrexone, may have a place in the long-term management of this problem.<sup>7</sup> When compared with naloxone, nalmefene is substantially more bioavailable when given by mouth, it has a more potent antagonist action at opioid receptors, and it is metabolized more slowly (longer plasma half life).<sup>15</sup> An open label trial of nalmefene for chronic pruritus of cholestasis<sup>15</sup> has suggested that this drug may be efficacious in reduced scratching activity. Naltrexone may be an alternative to nalmefene in this context.<sup>29</sup> However, the administration of naltrexone has been associated with hepatotoxicity,<sup>30</sup> and it seems to be less well tolerated than nalmefene by some patients with chronic cholestasis (Jones EA, unpublished observations, December 1998). Precipitation of a clinically significant opiate antagonist-induced opioid withdrawal-like reaction in cholestatic patients<sup>8</sup> may be avoided or minimized by starting oral therapy with small doses and gradually increasing the dose until a therapeutic effect is achieved.<sup>15</sup>

**Serotonin Receptor Subtype Antagonists.** Anecdotal reports have suggested that the 5-HT<sub>3</sub> serotonin receptor subtype antagonist, ondansetron, may ameliorate the pruritus of cholestasis.<sup>31,32</sup> Moreover, in a controlled trial, administration of ondansetron, but not a placebo, appeared to be followed by transient ameliorations of pruritus in cholestatic patients.<sup>33</sup> At least three factors limit the impact of this trial: (1) it was not double-blind, (2) a subjective primary efficacy endpoint was used, and (3) the drug was administered as a single intravenous bolus injection, thereby ensuring that any effect attributable to the drug would be transient. In a placebo-

controlled, double-blind, cross-over trial, ondansetron administered orally for 1-week periods was associated with a modest decrease in a visual analogue score of the perception of pruritus, which did not seem to be clinically significant.<sup>34</sup> Ondansetron may influence the pruritus of cholestasis by modulating central opioidergic neurotransmission,<sup>19,20</sup> by decreasing serotonergic neurotransmission, or both. Gastrointestinal symptoms, notably effects of decreased intestinal transit time, may limit the use of ondansetron in cholestatic patients.

#### Liver Transplantation

Currently available treatment options for the pruritus of cholestasis do not enable adequate relief of the symptom to be achieved in all cases. Unrelieved pruritus can not only cause severe sleep deprivation, but may also lead to suicidal ideation. Indeed, in some patients with the pruritus of cholestasis the quality of life may be so poor that liver transplantation may be considered irrespective of evidence of hepatic decompensation or indices of prognosis.

#### CONCLUDING PERSPECTIVES

The hypothesis that increased central opioidergic tone contributes to pruritus complicating cholestasis is supported by findings that strongly suggest (1) opiate agonists induce pruritus of central origin,<sup>4,5</sup> (2) opioidergic tone in the central nervous system is increased in cholestasis,<sup>8,9</sup> and (3) opiate antagonists reduce scratching activity in patients with the pruritus of cholestasis.<sup>13-15</sup> The observation that rifampin induces an opiate withdrawal syndrome in patients on maintenance doses of methadone<sup>35</sup> raises the possibility that apparent ameliorations of the pruritus of cholestasis induced by rifampin<sup>25-27</sup> may be attributable to an effect of rifampin on the opioid neurotransmitter system, which leads to a decrease in opioidergic tone. Apparent ameliorations of the pruritus of cholestasis after the administration of propofol<sup>36,37</sup> may also be attributable to a modulation of opioidergic tone.<sup>38</sup> The available data do not indicate which endogenous opioid receptor ligands may be responsible for contributing to the pruritus or which opiate antagonists may be optimal for use in its short-term or long-term treatment. Only interactions between certain opioid peptides and certain opioid receptor subtypes may be relevant to the pruritus of cholestasis. The sites of synthesis of endogenous opioids involved in the mediation of the pruritus of cholestasis are currently unknown, but one source may be the cholestatic liver itself.<sup>39</sup> There may be increased plasma-to-brain transfer of endogenous opioid peptides in cholestasis<sup>40</sup> as a consequence of their accumulation in plasma,<sup>8,10</sup> and this process would be facilitated by their amphoteric properties. However, the potential relevance of this phenomenon to the pathogenesis of the pruritus of cholestasis remains to be determined. Whether opioid receptors on peripheral neurons are involved in the pathogenesis of the pruritus of cholestasis is uncertain. Furthermore, there is currently a paucity of data that indicate that peripheral events in the skin initiate the neuronal events that mediate the pruritus of cholestasis. Nevertheless, a contribution to pathogenesis from neuronal events originating in peripheral cutaneous nerve fibers cannot be excluded.

Opiate antagonists, which are bioavailable when given orally, such as nalmefene and naltrexone, would appear to have potential for use in the long-term management of the pruritus of cholestasis.<sup>8,15,29</sup> However, administration of opi-

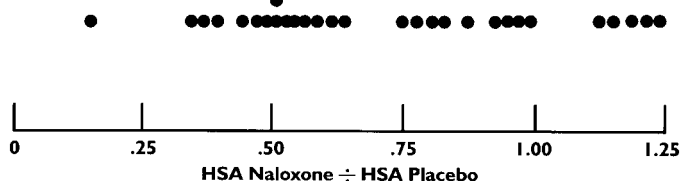


FIG. 1. Distributions of ratios of mean hourly scratching activity (HSA) during 24-hour intravenous infusions of naloxone (HSA Naloxone) to that during 24 intravenous infusions of placebo (HSA Placebo) in 29 patients with the pruritus of cholestasis. The study was randomized and double-blind. The geometric mean hourly scratching activity of each patient during naloxone infusions was divided by the corresponding mean during placebo infusions. The therapeutic advantage of naloxone over placebo is indicated by values of the ratio below 1.0. The mean ratio (0.727) is significantly less than 1.0 ( $P < .001$ ), the expected value if naloxone had no beneficial effect on scratching activity. Reprinted with permission of the Annals of Internal Medicine.<sup>14</sup>

ate antagonists for this indication is currently still experimental and the availability of drugs of this class does not obviate the use of conventional empiric therapies.

Altered function of other neurotransmitter systems, such as the serotonin system,<sup>33</sup> may also contribute to the pruritus of cholestasis. However, at this time the efficacy of serotonin receptor subtype antagonists in the treatment of the pruritus of cholestasis has not been established.

Some patients with severe pruritus associated with cholestatic disorders have not experienced substantial relief from the perception of pruritus over the short term after oral administration of either an opiate antagonist (nalmefene or naltrexone) or ondansetron. However, dose-response data are sparse.

There is still a paucity of definitive data on the mechanisms involved in the mediation of the pruritus of cholestasis. It remains possible that mechanisms other than altered function of the opioid and serotonergic neurotransmitter systems may be implicated.

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