

## Primer of Postoperative Pruritus for Anesthesiologists

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**Postoperative itching is an important problem in the postoperative care unit. Pruritus after surgery may be drug induced (including intrathecal opioids) or secondary to a preexisting systemic disease. Mechanisms of itching are complex and not completely understood. The purpose of this review is to highlight new discoveries in pathways and mechanisms of pruritus and to summarize up-to-date knowledge about treatment of itching after surgery. More basic and clinical studies are needed to address the effects of drugs on specific receptors and improve the treatment of postoperative pruritus.**

**UNDERSTANDING** different mechanisms of pruritus is necessary to diagnose and treat postoperative pruritus. *Pruritus* is an unpleasant, localized or generalized sensation on the skin, mucous membranes, or conjunctivae, which the patient instinctively attempts to relieve by scratching or rubbing. Itching is a disturbing feeling (or sensation), and scratching is the response (or action). Itch can be induced by nonpathologic conditions such as the movement of a hair, whereas pruritus represents a condition in which itch is present without a normal cause.

The origin of pruritus can be cutaneous (pruritoceptive), neuropathic, neurogenic, mixed, or psychogenic.<sup>1-6</sup> The use of opioids intrathecally or epidurally frequently results in itching. This uncomfortable adverse event requires the use of therapeutic agents in most circumstances, which can be ineffective or even reverse the analgesic effect of the opioid.

Several systemic and skin diseases are associated with

pruritus. There is still much unknown about postoperative itching in patients with diseases associated with pruritus, *e.g.*, (1) the incidence of pruritus after receiving opioids *via* the neuraxial route, (2) whether the use of opioids in patients with these disorders would potentiate their pruritus, (3) whether the development of pruritus in these patients when treated with neuraxial opioids is a side effect of the opioid or the natural manifestation of the disease.

The purpose of this review is to facilitate an understanding of the pathways and mediators involved in the development and central transmission of the itch sensation, to describe the methods available to evaluate itch, and to provide a basis for its rational therapy. We also wanted to summarize the up-to-date knowledge about systemic diseases that have pruritus as a symptom and may be associated with an increase in the incidence of pruritus in the perioperative period.

### Pathways

The mechanisms of pruritus have been poorly understood in the past because it was considered solely from the neurophysiologic point of view as a submodality of pain. However, more recent studies have shown that pain and pruritus are sensations transmitted through different populations of primary sensory neurons. A subclass of C-nociceptors, which is mechano-insensitive and histamine-sensitive, transmits itch.<sup>7</sup> These fibers, which originate in the skin at the junction of the dermis and epidermis, have thin axons but extensive terminal branching. These unmyelinated C-fibers transmit itch impulses to the ipsilateral dorsal horn of the spinal cord,<sup>3</sup> where they synapse with itch-specific secondary neurons. These secondary neurons immediately cross over to the opposite anterolateral spinothalamic tract<sup>3</sup> to the thalamus and then to the somatosensory cortex of the postcentral gyrus<sup>6</sup> (fig. 1). C-fibers that mediate itch have extremely low conduction velocities (mean, 0.5 m/s), approximately half those of mechano-heat nociceptors, and receptor fields that are approximately three times larger (up to 85 mm in diameter).<sup>7-9</sup> This pathway is the only one identified so far, but others not yet discovered may exist.

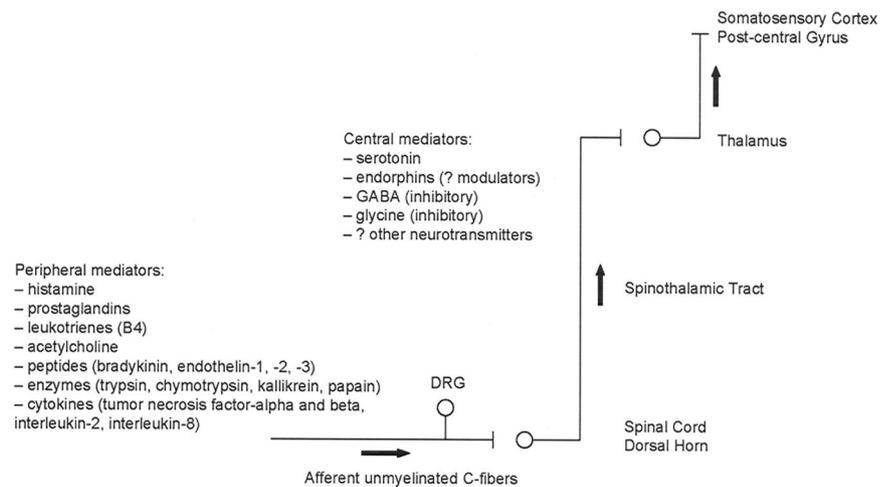
When histamine induces itch, it activates both the

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**Fig. 1. Afferent itching pathways.** Primary neurons consist of unmyelinated subclass of C-nociceptors (mechano-insensitive and histamine-sensitive) that synapse with itch-specific second-order neurons in dorsal horn of the spinal cord. The secondary neurons immediately cross over to join opposite antero-lateral spinothalamic tract and travel to the thalamus, where they synapse with third-order neurons. These third-order neurons travel to the somatosensory cortex of the postcentral gyrus. DRG = dorsal root ganglion; GABA =  $\gamma$ -aminobutyric acid.



anterior cingulate cortex, thus both the sensorial and emotional aspects of itch, and the supplemental motor area. The latter is thought to participate in the preparation of the scratching response.<sup>10-12</sup> Although the itch sensation seems to be transmitted by a subset of C-fibers, which, as described above, are different from those involved in the transmission of pain, increasing evidence supports an interrelation between these two distinct sensations. Painful stimuli, such as thermal, mechanical, or chemical, can inhibit itching,<sup>13</sup> and inhibition of pain processing may enhance itch.<sup>14</sup> In addition, it has been shown that the mechano-insensitive, histamine-sensitive nerve fibers are “selective” but not “specific” for pruritogenic substances. The pruritic potency of a mediator increases with its ability to activate mechano-insensitive, histamine-sensitive nerve fibers (itch receptors) but decreases with activation of mechano-responsive, histamine-insensitive fibers.<sup>15</sup> One interesting hypothesis is that there are two types of histamine-sensitive primary afferent neurons:<sup>16</sup> One type enhances pruritus, whereas the other attenuates it.

## Mediators

Several substances have been identified as mediators of itch that can stimulate the mechano-insensitive, histamine-sensitive nerve fibers involved in itch transmission.

### Histamine

Histamine can stimulate various nerve endings. When applied into the epidermis, it causes itch; when applied more deeply into the dermis, it evokes pain, sometimes accompanied by itching.<sup>17</sup> To induce itch, histamine directly stimulates type 1 histamine (H1) receptors on the itch-specific C-fibers.<sup>7,18</sup> However, only a few types of itch can be relieved by antihistamines because only a few, such as insect bites, most forms of urticaria, cutaneous mastocytosis, and allergic skin reactions, are caused by histamine release in the skin. Approximately

85% of histamine receptors in the skin are of the H1 subtype, and the remaining 15% are H2 receptors.<sup>19</sup> Wheal-and-flare reactions may be associated with itching. The addition of an H2 receptor antagonist to an H1 receptor blocker augments the inhibition of a histamine-induced wheal-and-flare reaction. Therefore, H2 receptor antagonists have been combined with H1 receptor antagonists in the treatment of chronic urticaria<sup>20</sup> and burn-wound itch.<sup>21</sup>

### Prostaglandins and Leukotrienes

Prostaglandins elicit very little or no pruritus when applied to the skin,<sup>22,23</sup> but they serve an important synergistic function in itching.<sup>24,25</sup> When administered in combination with histamine, prostaglandins potentiate the histamine-elicited itch. On the other hand, it seems that prostaglandins are potent itch-producing substances in the conjunctiva,<sup>26,27</sup> and the antiitch efficacy of ketorolac in allergic conjunctivitis seems to involve inhibition of conjunctival prostaglandin synthesis from arachidonic acid.<sup>28</sup> Leukotriene B4 induces itch-associated responses when injected intradermally, suggesting that leukotriene B4 may be an endogenous mediator of itch in the skin.<sup>29,30</sup>

### Acetylcholine

Acetylcholine is released from cholinergic nerves in the skin. The intradermal injection of acetylcholine elicits burning pain in humans<sup>31</sup> and evokes responses in nociceptive fibers in the superfused skin-saphenous nerve preparation of the rat.<sup>32</sup> In patients with atopic eczema, the intradermal injection of acetylcholine produces predominantly pruritus,<sup>31,33</sup> rather than the usual burning pain. This pruritogenic action of acetylcholine seems to be mediated by the activation of M3 muscarinic receptors in the skin<sup>34</sup> and is independent of histamine.<sup>35</sup>

### Serotonin

Serotonin (5-hydroxytryptamine [5-HT]) is an important neurotransmitter involved in a wide range of neu-

romodulatory processes in the central nervous system by acting on a number of 5-HT receptor isoforms. Three patients with generalized pruritus (resistant to other therapies) were treated effectively with 5-HT<sub>3</sub> receptor antagonist.<sup>36</sup> The success of this treatment led to the hypothesis that serotonin, acting *via* 5-HT<sub>3</sub> receptors, is involved in the generation or sensation of pruritus.<sup>36</sup> Ondansetron, a selective serotonin 5-HT<sub>3</sub> receptor antagonist, has been shown to be effective in the treatment of spinally or epidurally administered opioid-induced pruritus by some investigators<sup>37-39</sup> but not by others.<sup>40,41</sup>

### Peptides

Bradykinin is a pain-producing and proinflammatory nonapeptide that activates a subpopulation of polymodal nociceptors.<sup>42,43</sup> As such, bradykinin not only produces pruritus,<sup>44</sup> but also enhances the effect of interleukin 2-induced pruritus on sensory nerves.<sup>45</sup> Bradykinin is a poor histamine releaser. The administration of endothelin 1, endothelin 2, and endothelin 3 in human skin *in vivo* resulted in a dose-dependent area of pallor surrounded by a long-lasting flare, accompanied by a short-lived burning pruritus that seemed not to be mediated by histamine release from mast cells.<sup>46,47</sup> However, there are no pathologic conditions where endothelins have been implicated as mediators of pruritus. Substance P is another peptide that elicits itch sensation in human subjects when applied to the skin.<sup>48,49</sup> Substance P is a histamine releaser.<sup>50</sup> This peptide is speculated to be involved in hemodialysis-associated pruritus<sup>51</sup> and the pruritus of atopic dermatitis<sup>52</sup> and psoriasis.<sup>53</sup> Other peptides, such as neurotensin, vasoactive intestinal peptide, somatostatin, and melanocyte-stimulating hormone, are thought to mediate pruritus by releasing histamine from dermal mast cells.<sup>54,55</sup>

### Enzymes

Many physiologic processes (such as inflammation) are the result of a delicate balance between proteases and their inhibitors. If the balance is disturbed, pathologic processes (including pruritus) may result. Endogenous proteases, such as mast cell chymase or tryptase, have also been implicated in pruritogenic processes.<sup>56</sup> Experimentally, proteases such as trypsin, chymotrypsin, kallikrein, and papain can induce pruritus if injected into the epidermis.<sup>44,57,58</sup>

### Cytokines

Many physiologic and pathologic inflammatory processes are mediated by cytokines. Cytokines are low-molecular-weight, secreted proteins that mediate inflammatory signals between cells. One cell secretes a cytokine that elicits a cellular response from another cell. Some cytokines (such as tissue necrosis factor  $\alpha$ ) are synthesized early in response to various stimuli. These cytokines may stimulate specific cells to secrete

chemotactic cytokines (chemokines). Chemokines initiate the migration of inflammatory cells (from the vascular space to the inflammatory site). For example, tumor necrosis factor  $\alpha$  experimentally stimulates specific cells to release the chemotactic cytokine interleukin 8. This chemokine stimulates neutrophils to move into the inflammatory site. Cytokines (including interleukin 2, tumor necrosis factor  $\alpha$ , tumor necrosis factor  $\beta$ , eosinophil products) are mediators of pruritus. For example, in Sézary syndrome, the malignant cells may be the source of a cytokine, interleukin 2,<sup>6</sup> which may induce pruritus<sup>8</sup> (see Hematologic Diseases section).

## Drug-induced Itching in Anesthesia

### Opioid-induced Itching

Stimulation of itching may be physical or chemical. Physical factors such as pressure (from compression stockings) can stimulate itching. Chemically induced itching may be caused by systemic or neuraxial administration of an opioid. Systemic administration of opioids may stimulate opioid receptors in the skin. Itching may also be induced by neuraxial administration of exogenous opioids. Both systemic and regional opioids can cause itching by their actions on centrally located receptors.

**Systemic.** Histamine is a key mediator in itching produced by opioids administered systemically. Morphine, codeine, and meperidine<sup>59</sup> can cause a nonimmunologic release of histamine from mast cells in the tissue. Opioid receptor antagonists diminish experimentally evoked histamine-induced itch of the skin.<sup>60</sup> Therefore, cutaneous opioid receptors may be involved in the sensation of itch. Other mediators (including interleukin 1 and substance P) may also cause pruritus by releasing histamine from mast cells in the skin. In the periphery, opioid agonists such as morphine and methadone (but not fentanyl or oxymorphone) cause local itching and a typical histamine wheal-and-flare response. This itch response to intradermal morphine is reduced by H1 antihistamines but not by naloxone, indicating that histamine release by intradermally injected opioids is not mediated by opioid receptors.<sup>5,61,62</sup> Histamine acts directly on H1 receptors on the unmyelinated free nerve (itch-selective) endings in the epidermis.<sup>1</sup> Also, serotonin may cause itching by acting directly on peripheral serotonin receptors. H2 blockers (including cimetidine) alone are not useful, but when H2 and H1 blockers are used together, H2 blockers may make H1 blockers more effective.<sup>1</sup>

**Neuraxial.** Opioid receptors in both superficial and deep dorsal horn neurons may be involved in signaling the sensation of itch.<sup>63</sup> The facilitation of superficial neuronal responses to histamine by applying low concentrations of morphine intrathecally and coupled with inhibition of deep dorsal horn neurons might underlie the pruritus that is often observed after epidural or intrathecal morphine.<sup>63</sup>

Postoperative itching after intrathecal or epidural opioids is an undesirable side effect of anesthesia and is caused by many complex mechanisms. The central mechanism of intrathecal and epidural opioid-induced itching may be related to cephalad spread of the drug<sup>64</sup> in the cerebrospinal fluid and its action on the medullary dorsal horn and a trigeminal nucleus in the medulla.<sup>65,66</sup> In monkeys, morphine injected unilaterally into the medullary dorsal horn causes ipsilateral facial scratching, which is probably mediated by  $\mu$ -opioid receptors.<sup>5,65,66</sup> Contralateral facial scratching seems to be related to neural mechanisms (including perhaps a change in the neural activity).<sup>66,67</sup> Therefore, opioids that do not cause histamine release can still cause itching by other mechanisms.<sup>1</sup>

Opioids also act in areas of the brain (probably medulla oblongata) to cause itching<sup>5</sup> and elsewhere, probably in the midbrain, to reduce itching.<sup>64,67</sup> Naloxone, the classic  $\mu$ -receptor antagonist, is effective in preventing or treating intrathecal or epidural opioid-induced itching. However, at higher doses, naloxone can increase postoperative pain.<sup>1,4,5</sup>

Intrathecal or epidural opioid-induced itching may be related to opioids acting as antagonists<sup>5</sup> to inhibitory central neurotransmitters ( $\gamma$ -aminobutyric acid and glycine). Neuraxial opioids can also cause itching by acting on central 5-HT<sub>3</sub> receptors. These receptors are concentrated in the dorsal horn of the spinal cord<sup>68</sup> and the trigeminal nucleus of the medulla.<sup>69</sup> In addition, substance P<sup>60</sup> is an important central neurologic mediator that helps to modulate itching and pain despite being a peripheral histamine releaser. Substance P is present in C-fibers of the dorsal root ganglia, substantia gelatinosa in the spinal cord, and the brain (trigeminal nuclei, amygdaloid nuclei, and preoptic nuclei). A recent hypothesis<sup>3</sup> suggests that there are itching-selective neurons in the spinothalamic tract that respond to histamine.

Because intrathecal or epidural opioids do not produce itching by the release of histamine, H1 blockers (such as diphenhydramine) have little effect on centrally induced itching.<sup>1,5</sup> However, diphenhydramine may produce a sedative effect, which could be helpful. Nalbuphine, a  $\mu$  agonist-antagonist,<sup>5,70</sup> has also been used to prevent pruritus, but it has been associated with drowsiness.<sup>5</sup> Several investigators examined whether ondansetron is effective against pruritus with mixed results. Borgate and Stirnemann<sup>37</sup> demonstrated that ondansetron is effective in treating intrathecal or epidural morphine-induced pruritus. Others<sup>38</sup> demonstrated that the prophylactic use of ondansetron significantly reduces the incidence of intrathecal morphine-induced pruritus. Gurkan and Toker<sup>39</sup> have shown that ondansetron reduces the incidence of intrathecal fentanyl-induced pruritus. However, Yazigi *et al.*<sup>40</sup> found that ondansetron did not reduce intrathecal opioid-induced itching (morphine-sufentanil) after cesarean delivery. More recently, the incidence of pruritus after intrathecal sufentanil was also found not to be

reduced by ondansetron.<sup>71</sup> It is possible that ondansetron could not reach serotonin receptors<sup>4,41,71</sup> before the highly lipophilic compound sufentanil.

Drugs that may decrease itching without affecting the  $\mu$  receptor<sup>5,72</sup> have been the subject of multiple investigations. Propofol was used in an attempt to prevent or treat intrathecal opioid-induced pruritus. Propofol depresses posterior horn transmission in the spinal cord, which may reduce itching, but these trials yielded mixed results.<sup>5</sup> Droperidol, a dopamine D2 receptor antagonist, has been used to decrease the excitatory side effects of intrathecal opioids. Droperidol may also be a weak serotonin receptor antagonist,<sup>5</sup> but its application is controversial because the U.S. Food and Drug Administration recently has issued a warning about cardiac arrhythmias.<sup>73</sup> Methoxybenzamide (such as metoclopramide and alizapride) have also been tested. Alizapride does not decrease the incidence but may reduce the intensity of itching.<sup>72</sup>

#### *Antibiotics*

**Penicillin.** Patients who are allergic to penicillin when exposed to this antibiotic may manifest an immediate type I hypersensitivity reaction.<sup>74</sup> The reaction is triggered by histamine release from mast cells, which are sensitized by immunoglobulin E with a specific affinity for the antibiotic. Classically, this reaction may include itching, bronchospasm, and hypotension and may be life threatening.

**Vancomycin.** Rapid systemic intravenous administration of vancomycin causes a massive nonimmunologic release of histamine. Red man syndrome, the most common adverse reaction to vancomycin therapy, consists of flushing, pruritus, chest pain, muscle spasms, or hypotension that develop during vancomycin infusion.<sup>75,76</sup> The onset may occur within a few minutes and usually resolves within 20 min but may persist for several hours. One of the most important factors that affects the incidence of adverse reactions is the vancomycin infusion rate. It is recommended that vancomycin should be administered in a dilute solution over a period of no less than 60 min to avoid rapid infusion-related reactions. Vancomycin directly releases histamine from mast cells by a nonimmunologic process,<sup>77,78</sup> and red man syndrome is most likely a consequence of histamine release. The occurrence of pruritus during vancomycin administration can help the physician to identify at an early stage those patients who are at risk for hypotension.<sup>79</sup> Muscle relaxants and opioids may potentiate vancomycin-induced histamine release.<sup>80,81</sup> Antihistamines attenuate histamine-mediated side effects of vancomycin.<sup>82</sup>

**Rifampin.** Rifampin, a semisynthetic antibiotic derivative of rifamycin, is associated with cutaneous reactions that are in general mild and self-limiting. These reactions consist of flushing and itching with or without rash. In addition, rifampin, given either intravenous or orally,

potentially causes moderate pruritus that resolves when rifampin is discontinued.<sup>83</sup>

**Hetastarch.** Hetastarch is a high-molecular-weight hydroxyethyl starch that belongs to a group of colloids that structurally resemble glycogen. It is most frequently used to expand the intravascular volume in hypovolemic patients. Administration of hetastarch is associated with several complications, including transient increases in serum amylase, anaphylactoid reactions, coagulopathy, and pruritus.<sup>84-86</sup> Topical capsaicin has been used to treat hetastarch-induced pruritus.<sup>84</sup>

**Other Drugs.** In some situations, various local anesthetics may either increase or decrease itching. Fentanyl is associated with less severe pruritus when mixed with bupivacaine in obstetric patients.<sup>87</sup> However, intrathecal fentanyl is associated with more severe pruritus<sup>88</sup> when mixed with procaine instead of lidocaine or bupivacaine. In one study<sup>16</sup> of volunteers, local infiltration of 2% chloroprocaine increased the itching produced by intradermal histamine. The local anesthetic may block the histamine-sensitive primary afferent neurons that decrease pruritus.

Drug-induced intrahepatic cholestasis may also cause pruritus.<sup>89</sup> This pruritus is associated with phenothiazines, estrogens, tolbutamide, anabolic steroids, and other drugs. Withdrawal of the drugs and administration of prednisolone<sup>90</sup> and ursodeoxycholic acid<sup>90</sup> may improve the liver dysfunction.

## Itching in Different Anesthetic Environments

### *Assessment of Itching*

Common postoperative symptoms, such as nausea, pain, and itching, are important in anesthetic practice. More ambulatory surgery is being done now, and problems such as itching present more commonly in ambulatory surgery patients.<sup>91</sup> For example, spinal anesthesia using low-dose lidocaine (and intrathecal opioids) is now used for some ambulatory procedures because patients recover motor and sensory function quickly.<sup>71</sup> However, itching is associated with neuraxial opioids; its incidence ranges between 30% and 100%.<sup>5</sup> The incidences of itching after intrathecal and epidural sufentanil are 80% and 55%.<sup>5,92</sup> The respective incidences of itching after fentanyl are 67-100% and 67%, and those of morphine are 62-82% and 65-70%.<sup>5</sup>

Different approaches to assess postoperative itching have been in use. In some studies, qualitative scales are used, such as none, mild, moderate, or severe.<sup>38-40</sup> In other studies, severe itching is an accepted definition if treatment is needed.<sup>40</sup> Other studies have used visual<sup>37</sup> or verbal analog scales<sup>71</sup> with 0 being no pruritus and 10 being the worst pruritus the patient can claim. Symptom distress scores have been devised to evaluate how bothersome itching is to the patient. No assessment tool has been uniformly used to measure the intensity of pruritus.

Different approaches to evaluate the effectiveness of medications to treat postoperative itching have been used. In some studies, patients were treated if and when they requested medication,<sup>39,40,71</sup> whereas in others, patients were treated if their score was greater than 4.<sup>37</sup>

### *Postoperative and Acute Pain Management*

Postoperative pruritus (or itching) is an important problem in the postanesthesia care unit for the patient and the anesthesiologist. Acute postoperative pain management includes the systemic administration of opioids such as morphine, codeine, and meperidine. These drugs can cause a nonimmunologic release of histamine from mast cells in tissue<sup>59</sup> and can induce itching in patients in the postanesthesia care unit. Neuraxial administration of opioids may also cause itching. Patients with itching have been treated with diphenhydramine, ondansetron, propofol, nalbuphine, or naloxone. Diphenhydramine is more useful for itching produced by systemic opioids. Ondansetron has been used to combat itching due to neuraxial opioids, but studies of this agent disagree about its effectiveness. Small doses of propofol have been useful in treating pruritus. Naloxone and nalbuphine have been effective against neuraxial-induced itching. However, patients treated with naloxone may experience pain, and those treated with nalbuphine have drowsiness.

### *Obstetric Anesthesia*

Itching is present in 50% of parturients with intrahepatic cholestasis. It occurs mainly in the third trimester in 0.5-2% of the pregnancies.<sup>93</sup> Diagnosis is based on history and excludes other causes of itching. Serum bile acids are increased, and liver function test results may be abnormal. Fetal morbidity and mortality is high, and early delivery at 37-38 weeks may prevent complications. Itching resolves after delivery but may recur with subsequent pregnancies or with the administration of oral contraceptive drugs. In patients with severe pruritus or a history of complications in previous pregnancies, ursodeoxycholic acid treatment should be considered.<sup>94</sup>

The use of combined spinal-epidural technique for labor analgesia and anesthesia for cesarean delivery has increased. The intrathecal application of fentanyl, sufentanil, or morphine has increased the incidence of pruritus in laboring patients. The incidence of pruritus is higher in parturients and ranges from 60% to 100%,<sup>5</sup> depending on the type of opioid used, dosage, and amount of epinephrine added. The onset of pruritus begins shortly after analgesia. Pruritus with the lipid-soluble opioids, fentanyl and sufentanil, is of shorter duration and is dose dependent. The use of a minimal effective dose and addition of local anesthetics decreases the incidence and severity of itching. Pruritus with intrathecal morphine is of longer duration and difficult to treat. The epidural catheter placed for combined spinal-

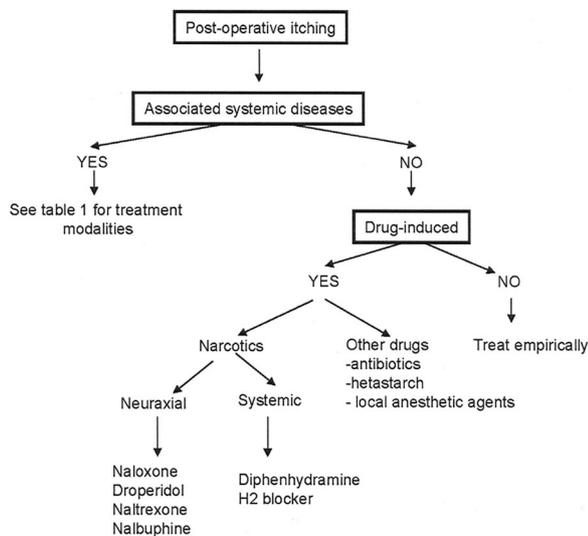


Fig. 2. Algorithm for management of postoperative pruritus.

epidural is used for pain relief during labor and delivery and after cesarean delivery. Administration of morphine epidurally is now a standard practice for postoperative pain relief after cesarean delivery. Its most common side effect, pruritus, occurs in 60% of patients. Propofol, naloxone, ondansetron, nalbuphine, and diphenhydramine have been used to treat morphine-induced pruritus.<sup>5</sup>

### Treatment of Pruritus Related to Anesthesia

Numerous treatments (fig. 2) have been tried to prevent or treat pruritus. Pruritus associated with preexisting systemic diseases is usually treated empirically (table 1). Systemic opioid-induced itching is usually treated with H1 blockers such as diphenhydramine. Numerous drugs are available for attempts to prevent or treat neuraxial opioid-induced itching. The treatment of itching induced by drugs other than opioids differs according to the drug involved and its mechanism of action.

Drugs used to prevent or treat neuraxial opioid-induced itching include lidocaine, propofol, droperidol, ondansetron, nonsteroidal antiinflammatory drugs, and  $\mu$ -opioid receptor antagonists.<sup>5</sup> Lidocaine causes sodium channel blockade,<sup>94,95</sup> which may help to attenuate pruritus. Intravenous lidocaine (intermittent intravenous boluses, typically 100 mg, or 100-mg intravenous bolus followed by infusion at  $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) has been advocated to treat pruritus.<sup>5,95,96</sup> Propofol has been used to treat pruritus (10-mg intravenous bolus alone, or same intravenous bolus followed by infusion at  $0.5\text{--}1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ).<sup>5,97,98</sup> Ondansetron, 8-mg intravenous bolus, has been tried to prevent itching, with controversial results. Nonsteroidal antiinflammatory drugs (e.g., diclofenac, tenoxicam) inhibit cyclooxygenase and may have preventive effects.<sup>5</sup> Droperidol depresses nerve transmission, inhibits serotonin receptor activation,<sup>5</sup> and

effectively prevents pruritus.<sup>5,97</sup>  $\mu$ -opioid receptor antagonists<sup>5,97</sup> also have similar effects.

An interesting meta-analysis of 22 trials (1,477 patients) was performed by Kjellberg and Tramer.<sup>97</sup> This analysis showed that prophylactic naloxone ( $0.25\text{--}2.4 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  intravenous), naltrexone (9 mg oral), nalbuphine (intravenous or epidural), or droperidol (2.5 mg intravenous) was effective. This meta-analysis also demonstrated that prophylactic propofol (intravenous), epinephrine (intrathecal or epidural), clonidine (epidural), prednisone (epidural), ondansetron (intravenous), or hydroxyzine (intramuscular) was ineffective. The meta-analysis demonstrated that there is “a lack of valid data on the efficacy of interventions for the treatment of established pruritus.”<sup>97</sup> This conclusion agrees with an excellent review of the literature by Szarvas *et al.*<sup>5</sup>

There is not enough basic research on pruritus<sup>99</sup> or appropriate animal models.<sup>99</sup> There are many reasons for the inconclusive results in the clinical studies of agents that may prevent (or treat) pruritus. Studies do not use uniform approaches to evaluate pruritus or its treatment. Because itching is a subjective symptom, it is difficult to design these studies. Evaluating the antipruritic activities of a drug (such as droperidol or propofol, which also sedates patients) is even more complex.<sup>5</sup> In addition, there have not been enough studies to clarify the underlying pathobiology of the mechanisms of pruritus. Pruritus is probably the end result of multiple mechanisms. Therefore, one drug may not be able to block all the itching from intrathecal or epidural opioids. There are many small studies with too few patients that cannot be compared because the designs differ. Larger and better-designed investigations are needed to provide more accurate data to develop a better paradigm for treatment of the patient with postoperative pruritus.

### Itching in Coexisting Diseases that May Alter Anesthetic Choice or Treatment of Pruritus

The mechanisms of itching in these diseases are poorly understood and may differ in each condition (table 1). A brief sketch of some examples follows.

#### Renal Diseases

Pruritus occurs in 25–86% of patients with chronic renal failure.<sup>100,101</sup> One third of uremic patients—not treated with dialysis—experience itching.<sup>102</sup> The incidence of pruritus is 70–80% in patients undergoing maintenance hemodialysis. This pruritus may be caused by the accumulation of pruritogens<sup>103</sup> such as histamine or serotonin. The incidence has decreased to 25% recently, probably because of the improvements in dialysis technique. Itching is absent in patients with acute renal failure.

**Table 1. Systemic Diseases Associated with Pruritus, Mechanisms, and Treatment Modalities**

Organ Systems	Disease	Proposed Mechanisms	Treatment Modalities	References
Renal	Chronic renal failure End-stage renal disease	Dryness of skin; impaired sweating; secondary hyperparathyroidism; ↑ plasma histamine; central modulation by ↑ serotonin; immunologic mechanisms	Cholestyramine, naltrexone, ondansetron, topical capsaicin, thalidomide, intravenous lidocaine, azelastine, erythropoietin, and electrical needle stimulation Renal transplantation (definitive)	100–105
Hepatic	Extrahepatic cholestasis Biliary system obstruction Intrahepatic cholestasis Primary biliary cirrhosis Pruritus gravidarum Sclerosing cholangitis Infectious hepatitis Drug-induced cholestasis	Pruritogens produced by liver; failure of liver to detoxify pruritogens; release of pruritogenic substances by ↑ bile acids; central modulation by ↑ serotonin; endogenous opioids	S-adenosylmethionine, ursodeoxycholic acid, cholestyramine, rifampin, codeine, prednisolone, ondansetron, oral guar gum, and phototherapy Liver transplantation (definitive)	89, 90, 106–111
Hematologic	Polycythemia vera Iron-deficiency anemia Hodgkin lymphoma Sézary syndrome Chronic lymphocytic leukemia Plasma cell dyscrasias Mycoïdes fungoides Mastocytosis	Poorly understood, may differ in each condition	Phlebotomy, cyproheptadine, pizotifen, cholestyramine, aspirin, interferon, alpha, H1 and H2 blockers, nifedipine, psoralen, radiation, and photochemotherapy	6, 8, 9, 113–118
Endocrine	Hyperthyroidism Hypothyroidism  Diabetes mellitus Multiple endocrine neoplasia IIA (Sipple syndrome) Carcinoid syndrome	Activated kinins Xerosis  Neuropathy, renal failure; autonomic dysfunction Unknown Histamine; serotonin; kallikrein	Treatment of underlying disease (hypothyroidism and hyperthyroidism)  Control of diabetes Aprotinin	1, 2, 6, 8, 9, 135–139
Nervous system	Various diseases Notalgia paresthetica	Unknown Increased dermal innervation	No effective treatment	119–129

Renal transplantation is the most definitive treatment for uremic itch.<sup>101</sup> The itching decreases even if there is loss of transplant function, as long as immunosuppressive therapy is continued. This observation supports the hypothesis that an immunologic mechanism<sup>102</sup> is responsible for itching. Antihistamines are not very effective, even though the concentrations of histamine are high in uremic patients. Moisturizers may provide some relief in patients with dry skin. Ultraviolet B phototherapy reduces vitamin A content in the skin and decreases itching.<sup>104</sup> Oral activated charcoal and cholestyramine, an anion exchange resin, absorb organic and inorganic compounds and remove pruritogenic chemicals from body fluids. Other therapeutic measures to reduce itching in uremic patients include naltrexone,<sup>6,8,9</sup> ondansetron,<sup>6,8,9</sup> topical capsaicin,<sup>6,9</sup> azelastin,<sup>9</sup> thalidomide,<sup>8,9</sup> intravenous lidocaine,<sup>9</sup> erythropoietin,<sup>9</sup> and electrical needle stimulation.<sup>9</sup> Subtotal parathyroidectomy may be helpful in relieving itching in some patients with secondary hyperparathyroidism.<sup>105</sup>

### Hepatic Diseases

Itching is observed in 20–25% of jaundiced patients with hepatobiliary disease associated with cholestasis.<sup>106,107</sup> Pruritus usually starts on the soles of the feet and the palms of the hands and spreads to the rest of the body.<sup>106,107</sup> In primary biliary cirrhosis, pruritus is the initial symptom and affects 100% of the patients. Viral hepatitis may also cause itching.

There is no treatment that works for all patients. Several drugs are used to treat itching of hepatic origin. Symptomatic therapies, such as antihistamines, sedatives, topical steroids, and anesthetics, have little effect. S-adenosylmethionine and ursodeoxycholic acid reverse or reduce cholestasis and decrease itching. Oral guar gum, a dietary fiber, decreases itching during pregnancy by binding to bile acids in the intestines and increasing fecal elimination.<sup>108</sup> Cholestyramine also reduces plasma and tissue concentrations of bile acids by binding with bile acids in the intestines.<sup>109</sup> The antibiotic rifampin inhibits hepatic bile uptake and decreases pruritus as

does ultraviolet B phototherapy twice weekly, but rifampin *per se*<sup>83</sup> also can induce itching. The opioid receptor antagonists (naloxone, nalmefene, and naltrexone) also decrease itching but may cause withdrawal<sup>110</sup> in opioid-dependent patients. Codeine causes pruritus relief without withdrawal symptoms. Propofol depresses spinal excitation by endogenous opioids. Ondansetron decreases hepatic pruritus, thus indicating that serotonin may have a role in the etiology of pruritus.<sup>111</sup>

The definitive mode of therapy for severe intractable pruritus is liver transplantation. Extrahepatic biliary obstruction caused by tumors can be treated by surgery, chemotherapy, or radiation therapy. Insertion of a stent in the bile duct during endoscopic retrograde cholangiopancreatography helps to drain bile and reduce both obstruction and pruritus within 24 h.

#### *Helicobacter pylori* Infection

*Helicobacter pylori* is an established cause of gastritis and has been implicated in extradigestive symptoms such as refractory pruritus. In one study, 10 patients with severe pruritus unresponsive to conventional therapy were evaluated for *H. pylori* infection. Eight had active infection. All 10 patients then received triple antibiotic therapy. Of 8 patients with active infection, 88% had some pruritus relief. Therefore, patients with *H. pylori* experience refractory pruritus that resolves after eradication of *H. pylori*.<sup>112</sup>

#### *Hematologic Diseases*

Generalized pruritus is associated with many diverse hematologic diseases, including polycythemia vera, iron-deficiency anemia, lymphomas, leukemias, plasma cell dyscrasias, mycoides fungoides, and mastocytosis. The mechanisms for pruritus in each condition may be different.<sup>6,8,9</sup>

The incidence of pruritus in polycythemia vera is approximately 50%,<sup>8</sup> but the cause of itching in these patients is unknown.<sup>6</sup> Many therapeutic modalities have been tried: phlebotomy or chemotherapy to reduce hematopoietic cell lines, cyproheptadine (antagonist of histamine and serotonin), pizotifen (antagonist of histamine and serotonin), cholestyramine aspirin, interferon alpha, and cimetidine.<sup>6,8,9</sup>

Hodgkin disease is a distinctive group of lymphomas characterized by unique distribution and histology.<sup>113</sup> Pruritus is a symptom classically associated with Hodgkin disease. It develops in approximately 30% of patients with Hodgkin lymphoma<sup>114-116</sup> and may precede the development of other symptoms by as much as 5 yr.<sup>117,118</sup> Pruritus in Hodgkin disease is controlled by effective treatment of the lymphoma itself with radiation therapy, chemotherapy, or both.<sup>6,8,9</sup>

The overall incidence of pruritus in non-Hodgkin lymphoma is low (approximately 3%).<sup>9</sup> However, almost all patients with T-cell lymphoma (Sézary syndrome) expe-

rience pruritus.<sup>8</sup> In mycoides fungoides,<sup>6</sup> which is a T-cell lymphoma in the skin,<sup>113</sup> pruritus may be induced by the release of mediators<sup>9</sup> from either the malignant cells or reactive cells. Effective treatment of the lymphoma itself<sup>6</sup> controls itching. However, symptomatic treatment of pruritus associated with lymphoproliferative disorders<sup>6,9</sup> also includes cimetidine (200 mg every 6 h) and prednisolone.<sup>6</sup>

#### *Metabolic and Endocrine Disorders*

Pruritus is also associated with various metabolic and endocrine disorders, including hyperthyroidism, hypothyroidism, diabetes mellitus, multiple endocrine neoplasia IIA (Sipple syndrome), and carcinoid syndrome. As is often the case, the mechanisms for pruritus in each condition may also differ.<sup>6,8,9</sup>

#### *Neurologic Disorders*

**Central Neurogenic Pruritus.** Central neurogenic pruritus is a rare symptom of central nervous system lesions such as multiple sclerosis,<sup>119-121</sup> spinal and cerebral tumors,<sup>122,123</sup> and cerebrovascular accidents.<sup>124,125</sup> Patients with multiple sclerosis may have paroxysmal attacks of itching.<sup>119-121</sup> In a study of dermatologic symptoms in 77 patients with brain tumors, 17% of patients reported pruritus.<sup>122,123</sup>

**Neurogenic Pruritus.** Patients with shingles (herpes zoster) often have painful rashes caused by reactivation of latent varicella-zoster virus in sensory ganglia.<sup>126-128</sup> This disease affects 10-15% of Americans, usually the elderly or immunocompromised. After resolution of the acute symptoms, some patients have development of chronic postherpetic neuralgia, whereas others have development of postherpetic itch, especially after facial shingles.

Notalgia paresthetica<sup>129</sup> is a sensory neuropathy involving the dorsal spinal nerves. The characteristic symptom is pruritus on the back, over or near the scapulae, occasionally accompanied by pain, paresthesia, and/or hyperesthesia. The cause remains unknown, but increased sensory dermal innervation<sup>126</sup> in the affected skin areas may contribute to the symptoms.

#### *Malignancy*

Various paraneoplastic syndromes are associated with solid tumors and are thought to be due to remote effects of the tumors. The mechanisms for paraneoplastic syndromes differ, but they rarely cause generalized itching.<sup>9</sup> The pathophysiology of this type of itching in these patients is not known.

#### *Human Immunodeficiency Virus-infected Patients*

Pruritus is one of the most common symptoms in patients with human immunodeficiency virus. Pruritus in these patients can develop as a consequence of dermatoses, such as papulosquamous disorders, skin infec-

tions, and drug reactions. It can be associated with systemic diseases, such as renal failure or liver disease, and can be a manifestation of progressive immunodeficiency and dermatoses peculiar to human immunodeficiency virus infection.<sup>130-134</sup> If no dermatologic cause is found, a systemic cause or medication-related etiology should be sought. Idiopathic human immunodeficiency virus pruritus is a diagnosis of exclusion and should only be considered when a specific diagnosis cannot be established.<sup>131</sup>

### Skin Diseases

Itch is a debilitating symptom that accompanies various skin diseases, such as atopic dermatitis, contact dermatitis, and urticaria.<sup>19,60</sup> Pruritus is the cardinal symptom of atopic dermatitis (eczema). H1 histamine receptor blockers are the drugs of choice to treat the itch; however, many pruritic diseases—except acute urticaria—respond poorly to H1 receptor blockers. The precise mechanisms and mediators of itch in most pruritic skin diseases are unclear.

### Conclusion

Postoperative itching can be the consequence of an undesirable effect of an anesthetic agent at a site not related to the anesthetic goal. Widespread use of potent opioids, especially *via* intrathecal and epidural routes, has increased the incidence of postoperative pruritus in recent years.

Postoperative itching may also be related to an underlying systemic disease. Patients may need anesthesia for surgical treatment of complications from the underlying systemic disease or other coexisting surgical problems and may run the risk of pruritus secondary to anesthesia as well. However, little is known about the influence of systemic diseases presenting with intractable pruritus on the incidence and severity of postoperative itching in this patient population. Considerable information is available about possible mechanisms of pruritus, but effective prevention and therapeutic modalities are often still missing. Aggressive treatment of postoperative itching could enhance patient satisfaction and shorten patients' stays in the postanesthesia care unit. More basic and clinical studies are needed to address the effects of drugs on specific receptors and improve the treatment of postoperative pruritus.

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