

Review

The pruritus of cholestasis

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Why do patients with cholestasis itch? The answer to this fundamental question is unknown. It is inferred that substances that accumulate in plasma and other tissues, as a result of cholestasis, cause pruritus; however, the specific nature of the substances and the mechanism by which they cause pruritus has not been discerned.

The absence of a clear rationale in studies of pruritus and the lack of techniques to study pruritus in human beings, and specifically, in patients with cholestasis have contributed to the vacuum of information on the pathophysiology and pathogenesis of the pruritus of cholestasis. Over the past 15 years, however, progress has been made in the study of pruritus by advancing the philosophy that research in pruritus, like in any other type of scientific area, requires valid methodology that provides objective data to be analyzed. In this context, the development of a system that allows for the conduct of behavioral studies of scratching activity, the behavioral manifestation of the sensation of itch, has satisfied the requirement of methodology. With the use of this technique, the role of the endogenous opioid system in the pathogenesis of the pruritus of cholestasis has been demonstrated.

1. The sensation of pruritus

The definition of pruritus is that of an unpleasant sensation that triggers the need to scratch [1]. In a study of 100 patients with atopic dermatitis the majority of the patients reported that scratching stopped with a feeling of satisfaction, disappearance of itch and appearance of pain [2]. These data may be relevant to patients with cholestasis who can also suffer from chronic pruritus and may suggest that scratching may be perpetuated by the pleasure it generates and inhibited by the pain it

generates in conditions characterized by chronic pruritus. The reported use of potentially harmful scratching tools (e.g. forks and knives) that cause harm do support the view that itch can transiently cease when pain is elicited by scratching.

2. Pathogenesis of pruritus

It is inferred that pruritus evolved as a sensation to lead to the protective reflex of scratching, as protection from a potentially harmful stimulus. Pruritus can result from the stimuli of polymodal (i.e. that respond to more than one type of stimuli) nociceptors (i.e. sensory fibers that respond to nociceptive stimuli). The stimulus associated with the sensation of pruritus is transmitted by unmyelinated C-fibers, which also transmit pain [3] (for review); however, neurons that respond only to histamine have been identified in human beings and have been defined as itch transmitting [4]. Electrophysiologic studies in animals identified single neurons that respond to histamine alone and neurons that respond to histamine and to mechanical stimulation, also involved in pain transmission [5]. These studies tend to support the existence of ‘two separate nociceptive channels’ [5], one for itch and one for pain. In this context, the importance of an animal model to study scratching behavior and to explore the pathophysiological mechanisms that support this behavior by the use of similar electrophysiological techniques seems to be a reasonable research goal.

3. Origin of the pruritus of cholestasis

Pruritus can be of central origin, as that associated with cerebral strokes [6,7] and multiple sclerosis [8]. Increased neurotransmission via the endogenous opioid system can result in pruritus. The classic example of this phenomenon is the pruritus that results from the central (e.g. intrathecal)

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administration of morphine [9,10]. Morphine binds to opioid receptors, in particular to the mu opioid receptor. Opiate antagonists (e.g. naloxone) can effectively relieve morphine-induced pruritus, supporting that the pruritus is opioid receptor mediated [9,10]. In laboratory animals (e.g. monkeys and rats), the microinjection of morphine into the medullary dorsal horn [11–13] is associated with scratching behavior, which has been interpreted to result from ‘pruritus’ in the animals. This behavior can be prevented by the administration of opiate antagonists again supporting that the scratching behavior is opioid receptor mediated [11,13]. Technical progress has allowed for studies from single-unit recordings in superficial lumbar dorsal horn neurons in rats, which have revealed that the intrathecal administration of morphine facilitated or depressed the response of some units to the intracutaneous injection of histamine and in some, the effect was naloxone reversible [14]. In summary, behavioral and electrophysiological data support a role of the endogenous opioid system in pruritus of central origin.

In cholestasis, there is evidence to suggest that central opioidergic tone is increased. The evidence can be summarized as follows: (i) patients with cholestasis can experience an unpleasant constellations of symptoms and signs suggestive of an opiate withdrawal reaction when administered opiate antagonists; this reaction in cholestasis has been termed ‘opiate withdrawal-like syndrome’ [15], (ii) a stereospecific naloxone reversible state of antinociception (analgesia) can be displayed by rats with cholestasis secondary to bile duct resection [16], and (iii) there is down regulation of mu opioid receptors in rats with cholestasis secondary to bile duct resection [17]. It was hypothesized that increased opioidergic tone in cholestasis mediates the pruritus; a central mechanism was proposed [18]. In this hypothesis, the pruritus of cholestasis would be analogous to the pruritus that results from the pharmacological increase in opioidergic tone by central morphine. That the pruritus of cholestasis is mediated, at least in part, by endogenous opioids, is supported by the amelioration of the pruritus by opiate antagonists. The reason for altered central neurotransmission in cholestasis is unknown, however, the liver may contribute to the increased availability of opioids in liver disease [19,20]. In this context, increased plasma levels of Met and Leu-enkephalins, two of the endogenous opioid peptides, have been reported in patients with liver disease, including those with primary biliary cirrhosis [21]. It is not known whether opioids derived from the liver in cholestasis mediate what has been interpreted as centrally increased opioidergic neurotransmission; however, transport proteins found in the basolateral domain of the hepatocyte are also found in the choroid plexus and in the blood brain barrier and can transport opiates in vitro [22,23] and may potentially transport periphery-derived opioids into the central nervous system (CNS). Furthermore, increased availability of

opioid peptides in the periphery may facilitate their entrance into the CNS [24].

4. Studies in patients with atopic dermatitis

An alternative and/or concomitant mechanism involving the central nervous system and that could support the chronic pruritus of cholestasis is central sensitization for itch. Central sensitization for pain or allodynia is recognized in patients with chronic pain, and it defines a state in which a non-painful stimulus around an injured area is perceived as painful [3]. In the context of pruritus, studies in subjects with atopic dermatitis, a condition characterized by chronic pruritus, have provided evidence for central sensitization for itch. In these studies, noxious stimuli (e.g. heat and mechanical, electrical and chemical stimulations) evoked pain in control subjects; in contrast, in patients with atopic dermatitis, the stimuli were perceived as itch [25]. Furthermore, sensitization to histamine, achieved by perfusion of this pruritogenic substance by microdialysis into the skin of a defined area of the forearm in normal control subjects, was associated with pruritus from chemical stimuli, although pain was still the dominant sensation, suggesting that chronic pruritogenic stimuli facilitate the perception of itch [25]. The triggering of itch by noxious stimuli was interpreted as resulting from central sensitization for itch, which would result from the constant pruritogenic (i.e. pruriceptive) input and which would not allow nociceptive stimuli to inhibit itch but to facilitate it. The timing of the appearance of itch, as described in these studies by patients with atopic dermatitis, has suggested that its mediation is via C-nociceptors [25].

Analogous to patients with atopic dermatitis, patients with chronic pruritus from cholestasis may undergo central sensitization for itch, so that noxious stimuli are experienced as pruritus by these patients. In this scenario, constant pruritogenic stimuli would result in continuous activation of C-pruriceptors, perhaps by pruritogens retained as a result of cholestasis. Indeed, spontaneously active itch fibers have been identified in a patient with chronic pruritus and prurigo nodularis in microneurographic recordings [26].

5. Behavioral studies in animals

Very interesting data emerging from a model of opiate-induced scratching in monkeys may provide some insight into central opioid-mediated pruritus and scratching behavior [27,28]. The scratching behavior associated with the administration of morphine into the MDH of monkeys was decreased by the co-administration of U50488H, a selective kappa agonist [27,28]. In addition, the administration of a kappa agonist prevented mu opioid receptor-mediated scratching in mice [29].

6. Central sensitization for itch and increased central opioidergic tone in the pruritus of cholestasis—a unifying model

The intrathecal administration of morphine inhibits pain but is associated with pruritus. This type of pruritus does not involve the stimulation of afferent (i.e. peripheral) pruriceptors and is, by definition, pruritus of central origin. It has been noted in experiments of neural recordings from single neurons [30] that spinal neurons that transmit pruritus information to the thalamus are not spontaneously activated [30], in contrast to the pain transmitting neurons, which are spontaneously active. It has been suggested that spontaneous activation of the pain pathway suppresses the activity of the neurons that transmit pruritus (i.e. inhibition) [31]. If the pain pathway is suppressed, by the administration of morphine (i.e. the pharmacological increase in opioidergic tone) the pruritus pathway may become activated and pruritus may be perceived. This switch in neurotransmission may explain central morphine-mediated pruritus. In cholestasis, increased central opioidergic tone may suppress the stimulation of pain-transmitting neurons and activate the central pruritus pathway (i.e. disinhibition). In this model, the administration of opiate antagonists would decrease pruritus. Indeed, the amelioration of the pruritus of cholestasis by opiate antagonists has been demonstrated in clinical trials that applied objective methodology, which tends to support the hypothesis that increased opioidergic tone, contributes to the pruritus of cholestasis [32–35]. In addition, central sensitization for itch, which could occur in cholestasis by the continuous stimulation of C-pruriceptors, may allow for non-pruritogenic stimuli to be perceived as pruritogenic, thus leading to chronic pruritus. The model proposed here involves peripheral and central events as possible mediators of the pruritus of cholestasis and support the implementation of therapeutic interventions that switch opioidergic tone to the non-pruritic mode (i.e. central mechanism) and that increase the threshold to the perception of noxious stimuli (i.e. peripheral mechanism).

7. Bile acids and the pruritus of cholestasis

Bile acids accumulate in the tissues of patients with cholestasis [36,37]. Bile acids were reported to elicit local ‘itch’ when injected intracutaneously in normal volunteers [38]; however, this model does not appear to be a model of the pruritus of cholestasis. Also, the oral administration of cholylsarcosine, a synthetic bile acid, to four patients with primary biliary cirrhosis (PBC) whose treatment with ursodeoxycholic acid (UDCA) had not been associated with normalization of serum activity of liver enzymes was reported to be associated with pruritus in one patient and worsening pruritus in another one [39]. This observation cannot be considered as evidence of a role of bile acids in

the pruritus of cholestasis as pruritus tends to be intermittent in cholestasis; furthermore, patients report exacerbations of pruritus in cholestasis after the intake of several substances including chocolate and meals rich in carbohydrates (NVBergasa, unpublished). The reported improvements of pruritus after invasive procedures (discussed under treatments) that remove substances from the circulation cannot be attributed to bile acid depletion because it is uncertain that only bile acids are removed. Furthermore, (i) in liver failure, when bile acids are maximally elevated, pruritus may cease [36], (ii) some patients with cholestasis and striking elevations of serum bile acids do not experience pruritus throughout the course of their disease, (iii) pruritus can fluctuate and even remit spontaneously without concomitant changes in serum bile acid concentrations and (iv) some patients with liver disease experience pruritus in the absence of increased concentration of bile acids in serum (at the time of that measurement). It is possible that a certain profile of serum bile acids is necessary for these substances to mediate pruritus but, based on current data, a role of bile acids in the mediation of the pruritus of cholestasis has not been proven.

8. Studies in molecular genetics

Not all patients with cholestasis report pruritus, regardless of the degree of cholestasis. This observation may suggest that the ability to perceive pruritus varies among individuals and that perhaps a genetic component is involved. In this context, genetic polymorphisms have been described in genes that code for hepatobiliary transport proteins. Studies aimed at the identification of genetic polymorphism in multidrug resistance protein (MRP) 2, which regulates the transport of organic compounds including dianionic conjugated bile salts [40,41] identified a single nucleotide polymorphism in MRP2 in patients with PBC and pruritus (Annarosa Floriani, 2005, personal communication). The relevance of this finding in the pathogenesis of the pruritus of cholestasis remains to be established.

The nuclear receptor pregnane X (PXR) mediates the induction of some of the cytochrome P450 (CYP) enzymes including CYP3A4 [42], of which bile acids are endogenous ligands, and the transporters MDR1 in the intestine [43] and MRP2 [44]. Rifampicin, phenobarbital and steroid hormones are ligands of PXR [45] [46]. The elucidation of pathways that control the gene expression of enzymes that metabolize xenobiotics, including cytochrome P450, transferases and transporters has facilitated the understanding on drug interactions in human beings [46]; however, any relationship that these findings (many of which have been derived from animal and in vitro experiments) may have to the pathogenesis and/or treatment of the pruritus of cholestasis has not been defined.

9. Pruritus in liver disease

Pruritus tends to be associated with cholestasis [47], as measured by increased activity of liver-derived alkaline phosphatase and plasma concentrations of bile acids; however, not all patients with cholestasis report pruritus, suggesting that a subject-dependent factor is necessary but, at present, unknown.

Primary biliary cirrhosis (PBC) is one of the liver diseases characterized by pruritus [47]. An internet-based survey of patients with PBC was conducted via the PBCers Organization, based in the United States with international membership, to identify patterns in the characteristics of pruritus (and fatigue). 242 subjects responded, 164 (68%) of whom reported pruritus (itch); 120 (74%) reported that their itch interfered with their sleep and 19 (11%), an important proportion, reported that nothing relieved the itch (Rishe and Bergasa 2002, unpublished).

A recent publication reported pruritus in 55 and 56% of patients with PBC enrolling in each of the two arms of a clinical trial of ursodeoxycholic acid (UDCA). [48]. It was reported in this publication that treatment with UDCA was not associated with a significant impact on the percentage of patients experiencing pruritus as compared to treatment with placebo. In a three-UDCA dose comparison study, which included 155 patients with PBC, 37% reported pruritus prior to enrollment into the study [48]. In this publication, it is reported that serum activity of alkaline phosphatase and Mayo risk score were independent predictors of the reporting of pruritus at baseline [48]. In one study, the intrahepatic florid bile duct lesion and granulomata correlated with pruritus in patients with PBC [49]. Pruritus can also be reported by patients with liver disease not typically associated with a 'serum liver profile' classic of cholestasis, including liver disease secondary to alcohol [50] and chronic hepatitis C [51–54].

10. Methodology for the scientific study of pruritus

Experienced investigators and clinicians have recognized the need for reliable methodology to study 'pruritus' [55,56]. Pruritus is a sensation; accordingly, it cannot be measured directly; however, pruritus invariably results in scratching behavior, which can be measured. The conduct of objective studies in pruritus had been prevented by the lack of objective methodology; this limitation has been overcome with the development of a scratching activity monitoring system (SAMS), which allows for the recording of scratching behavior independent from gross body movements [57]. The SAMS is based on piezoelectric technology, which permits the recording of vibrations produced by the fingernail in the act of scratching [57]. Portable versions of scratching activity monitoring systems have been developed [58,59]; thus, controlled clinical trials that incorporate objective quantitative methodology have been

possible for several years [32–35,60]. The interpretation of data obtained from subjective methodology is uncertain by the fact that different subjects perceive pruritus differently; thus, what is mild to some may be moderate to others. The inclusion of subjective methodology in behavioral studies of pruritus, however, may be used to gain insight on the relationship between perception and behavior on individual patients, as has been done in some studies [32–35,60]. In clinical medicine, if a given intervention is found not to reduce scratching activity in patients with the pruritus of cholestasis as studied in clinical trials, but has been found to decrease the perception of pruritus as measured by the visual analogue scale or by questionnaires, the clinician may opt to prescribe the intervention anyway, adopting the 'whatever gets one through the night is alright approach'. In scientific studies of pruritus, however, the realization that the placebo effect in pruritus studies is strong seems important for consideration.

11. Treatment of the pruritus of cholestasis

The approach to a patient with the pruritus of cholestasis includes the establishment of a diagnosis, the decision to treat the primary liver pathology and the hope to find an effective treatment to ameliorate or relieve completely the symptom. In conditions where the cause of cholestasis is reversible (e.g. some types of extrahepatic biliary obstruction), immediate intervention (i.e. relief of the obstruction) may be all that is needed. Some other times a potentially reversible cause (e.g. drug induced cholestasis without ductopenia) requires that the cause be identified and removed in the hope that cholestasis would resolve spontaneously. Unfortunately, diseases associated with cholestasis can be chronic and incurable. In these cases, the administration of approved treatments directed to treat the disease may not be associated with an amelioration of pruritus. A well recognized example of this situation is PBC, for which UDCA is the treatment approved, but in which this treatment is not associated with relief in pruritus in most cases. Thus, the specific management of the pruritus is necessary. In this context, the treatment of pruritus can be divided based on the expected effect, although a rationale is not always readily identified. The most common treatments currently used to treat pruritus are given in Table 1, accompanied by the references from which the recommendations were derived.

12. Selected treatment for the pruritus of cholestasis

12.1. Procedures aimed at the removal of pruritogens from the body

The non-absorbable anion exchange resins approved to treat hypercholesterolemia, cholestyramine [61],

Table 1
Selected treatments for the pruritus on cholestasis

Medication	Selected potential side effects	Dose/mode of administration/frequency	Ref.	Cost analysis
Cholestyramine	Bloating, constipation, malabsorption of nutrients and its complications including coagulopathy	4 g P.O. before and after breakfast; increase by 4 g at other meal times not to exceed 16 g/day	–	AWP of cholestyramine 4 gm/packet (60 packets total) ranges from \$83.61 to \$126.68
Phenobarbital	Sedation	3 mg/kg P.O. in divided doses	[90–92]	AWP 60 mg Tablet, 100 Tab \$9.29
Rifampicin	Hepatotoxicity	150 mg P.O./BID if serum bilirubin > 3 mg/dl; 150 mg P.O/ TID if serum bilirubin < 3	[93,94]	AWP of a 30 count bottle of rifampicin 150 mg ranges from \$36.95 to \$40.23.
Naloxone	Opiate withdrawal-like syndrome	0.2 µg/kg/min/ IV continuous infusions preceded by 0.4 mg IV bolus	[33]	
Naltrexone	Opiate withdrawal-like syndrome, potential hepatotoxicity	25 mg P.O./BID on day 1 followed by 50 mg P.O. daily	[78]	The AWP of naltrexone 50 mg for 30 count bottle ranges from \$128.25 to \$137.21.

AWP, Average wholesale price.

colestipol and colesevalan [62] are used to enhance the intestinal excretion of the pruritogen(s). This intervention counts on the excretion of the pruritogens(s) in bile; however, other possible mechanism can be considered in interpreting the antipruritic effect of cholestyramine. One observation in patients taking cholestyramine merits consideration. In patients in whom cholestyramine is effective, the effect may be transient. This phenomenon can be considered a form of tachyphylaxis, which tends to suggest a receptor-mediated effect. As cholestyramine intake is associated with the release of cholecystokinin (CCK) [63] and this hormone is an endogenous antiopiate, the antipruritic effect of cholestyramine may result from associated antiopiate neurotransmission [64]. This type of neurotransmission would be analogous to the administration of opiate antagonists. Behavioral studies in an animal model of cholestasis provided data in support of this idea [65].

The removal of pruritogens(s) that presumably accumulate in the plasma and tissues of patients with cholestasis and pruritus is the aim of invasive procedures, including plasmapheresis [66–68] [69] and more recently the technique of extracorporeal albumin dialysis (MARS) [54,70–72]. In interpreting the reported beneficial effect of these interventions as a treatment of pruritus, it is necessary to consider a placebo effect; thus, controlled clinical trials in the use of MARS and other invasive procedures are desirable, although indeed, they are difficult to design. The nature of the substances that are removed in the context of their pruritogenic effect is unknown at present.

Partial external diversion of bile [73] and ileal diversion [74] in children with chronic cholestasis and pruritus, have been reported to decrease pruritus to improve quality of life; however, percutaneous transhepatic biliary drainage, which resulted in a decrease in serum bile acids was reported to have no effect on pruritus [75].

12.2. Changes in opioidergic neurotransmission

The ameliorating effect of the pruritus of cholestasis by the administration of opiate antagonists including nalme-fene [21,34,35], naloxone [32,33,76,77] and naltrexone [78–80] supports the hypothesis that endogenous opioids contribute to the pruritus. The administration of continuous infusions of the opiate antagonists naloxone (0.2 µg/kg/min) preceded by 0.4 mg administered as an intravenous bolus was associated with a significant decrease in the mean hourly scratching activity and in the mean score for the perception of pruritus [32,33]. The ideal mode of administration of naloxone is parenteral, hence, not practical for chronic use; however, it is a useful alternative to manage patients with intractable pruritus. In these situations, patients can be hospitalized for intravenous infusions of naloxone, to be converted to oral naltrexone for follow up treatment. The available preparation of naltrexone is not ideal as the tablets are of 50 mg. One option to decrease the starting dose is to cut the tablets to provide less drug per dose (e.g. 12.5 mg), which can be increased if necessary. There are published concerns regarding hepatotoxicity with naltrexone [81]; thus, checking the serum hepatic profile on treatment is prudent. A recent study of naltrexone in patients with alcoholism did not report hepatotoxicity [82]. Naltrexone metabolites can accumulate in decompensated liver disease, which would require dose reduction; however, it is not common for patients with decompensated liver disease to report pruritus, as this symptom tends to cease as liver failure ensues [83]. An opiate withdrawal-like reaction [21,34,35] is a potential complication of the treatment of patients with cholestasis with opiate antagonists; accordingly, concern regarding the use of opiate antagonists in patients with cholestasis and pruritus exists. This reaction can be avoided by introducing opioid antagonism as intravenous naloxone at very low doses (0.002 µg/kg/min) by continuous infusion, gradually increasing the dose to 0.8 µg/kg/min depending on the

patients' response [84,85] and to start oral naltrexone at the lowest possible dose. The final oral dose depends on the response of the patient.

In view of the prevention of opiate-induced scratching behavior in laboratory animals by the pharmacological activation of kappa opioid receptors [28], the use of drugs with kappa agonist activity in the management of patients with the pruritus of cholestasis is an option, in light of the observations that support a role of increased opioidergic tone in the mediation of the pruritus of cholestasis. Butorphanol is an antagonist at the mu opioid receptor and an agonist at the kappa receptor [86]. The spray form of butorphanol (one application delivers close to 1 mg of drug) [87] was used in a patient with severe pruritus associated with chronic hepatitis C with marked reduction of the symptom and healing of cutaneous excoriations (NVBergasa, 2003, unpublished). The potential addiction to butorphanol, initially considered to be low [88], is important [89]; thus, the use of this drug for the treatment of the pruritus of cholestasis has to be considered in light of this possible complication.

12.3. Hepatic enzyme inducers and antibiotics

Phenobarbital [90–92] and rifampicin [93] are hepatic enzyme inducers used to manage patients with the pruritus of cholestasis. The reported decrease in pruritus associated with phenobarbital may be due to sedation, in part. The antibiotic rifampicin at doses between 300 and 450 mg/day [94] or 10 mg/kg [93] has been reported to improve the pruritus of cholestasis secondary to PBC as assessed subjectively. The mechanism of the reported antipruritic effect of rifampicin is unknown; however, rifampicin, which is also an antibiotic, induces drug-metabolizing enzymes and transporters, through activation of the pregnane X receptor [95]. Accordingly, the idea that the reported antipruritic effect of this drug results from either the enhanced metabolism of the 'pruritogens' or its transport may be considered. Furthermore, rifampicin may have antiopiate activity in conditions associated with increased opioidergic tone (e.g. cholestasis), based on a reported experience in patients maintained on methadone treatment [96]. Interestingly, rifampicin is associated with an increase in serum bile acids concentrations [97]. Rifampicin can be hepatotoxic at doses used to manage pruritus [98]; thus, follow-up of liver tests is necessary if this drug is to be prescribed. Another antibiotic, metronidazole, administered at doses of 250 mg orally three times a day for 1 week has been reported to control refractory cholestatic pruritus in patients with primary biliary cirrhosis [99]. Changes in gut flora by the antibiotic treatment that would result in changes in bile acid metabolism have been proposed to explain the reported beneficial effect of antibiotic treatment on this form of pruritus [99].

12.4. Anticholestatic agents

12.4.1. Bile acid therapy

In cholestasis of pregnancy, UDCA has been reported to decrease pruritus [100]; however, data from properly controlled studies are lacking [101].

13. S-Adenosylmethionine

The anticholestatic agent has been reported to decrease cholestasis and improve pruritus in patients with intrahepatic cholestasis of pregnancy [102,103].

13.1. Serotonin antagonists

The serotonin system participates in the mediation of nociception [104]. Variable results on the effect of ondansetron in the treatment of the pruritus of cholestasis have been published. Ondansetron was reported to decrease the pruritus associated with cholestasis in studies that applied subjective methodology [105–107], including a case of cholestasis of pregnancy [108]. Intravenous ondansetron (4 and 8 mg) and not placebo was reported to be associated with a decrease in pruritus in a small number of patients [107]. These results were not confirmed in a study that applied behavioral methodology [60].

13.2. Changes in threshold to experience nociception

In line with the idea that sensory perceptions may be perverted in patients with cholestasis and chronic pruritus, altering the threshold at which nociceptive stimuli are perceived may result in a decrease of the pruritus. In this category, two drugs have been used to treat the pruritus of cholestasis, as described below.

13.2.1. Dronabinol

Dronabinol is a sesame oil preparation of delta 9-tetrahydrocannabinol, the psychoactive compound extracted from *Cannabis sativa* L. (marijuana). Five milligram of dronabinol at bedtime to three patients with cholestasis and intractable pruritus was reported to be associated with a decrease in that symptom and improvement in sleep [109]. In interpreting the original report [110], the possibility of an increase in the threshold to noxious stimuli due to enhanced cannabinoid neurotransmission by the drug was suggested. This hypothesis was tested in an animal model of cholestasis secondary to bile duct resection (BDR). In this study, the pharmacological increase in cannabinoid neurotransmission was associated with an increase in the nociception threshold, as measured by the tail flick assay, in rats, which was significantly more prolonged in the BDR group than in the control group [111].

13.2.2. Gabapentin

Gabapentin is a drug used as adjunctive treatment of partial seizures with and without generalization, in adults with epilepsy [112] and in the treatment of neuropathies [113]. If central changes occur in patients with chronic pruritus leading to sensitization as reported in chronic pain, gabapentin may also decrease the perception of the former. Gabapentin was reported to abolish the symptom of brachioradial pruritus [114], a condition also characterized by dysesthesias [115]. Gabapentin was studied in a randomized double-blind placebo controlled study in patients with cholestasis and pruritus in which objective methodology was applied; however, preliminary analysis of the data does not suggest a therapeutic advantage of gabapentin over placebo.

13.3. Antidepressants

13.3.1. Sertraline

In a retrospective review, the use of sertraline (75 mg per day), a serotonin re-uptake inhibitor, was reported to be associated with improvement of pruritus in a small group of patients with PBC, who had recorded the perception of pruritus in their personal diaries as part of their participation in a clinical trial [116]. Any relationship between the reported effect of sertraline on pruritus and on mood is unknown at present.

13.4. Anesthetics

Propofol, an anesthetic reported to decrease pruritus induced by intrathecal morphine [117], has been reported to be associated with a decrease in the pruritus of cholestasis, at subhypnotic doses [117,118]. Years ago, lignocaine [119] was reported to improve this type of pruritus; considering the neural trajectory of pruritus, it is not difficult to conceive that some form of anesthesia may decrease the sensation of pruritus.

13.5. Phototherapy

13.5.1. To the skin

Phototherapy to the skin with ultraviolet (UV) light B is used by some clinicians to treat the pruritus of cholestasis. UV B treatment in erythemogenic doses is one of the treatments of psoriasis. There is no apparent rationale to use this intervention in the treatment of the pruritus of cholestasis. The effect of UV B treatment on the pruritus on this type of pruritus is highly questionable.

13.5.2. Bright light therapy directed towards the eyes

Patients with cholestasis and pruritus can display a 24-h rhythm in scratching activity, as detected in a placebo controlled study of naloxone infusions in which patients underwent continuous recording of scratching activity [33]. Circadian rhythms are of 24 or near 24 h duration and their most important regulator is light, via retinothalamic

pathways [120]. To explore whether light could alter the 24 h rhythm of scratching behavior, the effect of 10,000 lx of light indirectly reflected towards the eyes was tested in a pilot study of patients with pruritus secondary to chronic liver disease [121]. The light treatment was administered as prescribed in patients with seasonal affective disorder. Light exposures of up to 60 min in the morning and in the evening were associated with a decrease in the sensation of pruritus, a modest decrease in scratching behavior and a significant decrease in the variability of scratching at 8 weeks of treatment [121]. The decrease in the variability of scratching is a reflection of outbursts of 'pruritus' and may suggest that light therapy may be useful in conjunction with other medications. Bright light therapy has been associated with side effects, including episodes of mania; thus, administration under a proper schedule is necessary. A controlled study has not been conducted to test bright light therapy in the treatment of the pruritus of cholestasis.

13.6. Sedation and the use of antihistamines

A role of histamine in the pathogenesis of pruritus of cholestasis has not been confirmed; however, antihistamines, which lead to sedation, are widely used and can be associated with some relief in some patients.

13.7. Modalities that escape definition as antipruritogens

Other therapeutic modalities that have been used to treat the pruritus of cholestasis include flumecinol [122], antioxidants [123], and androgens [124]. In the context of steroid treatment, of prednisone has been used anecdotally to treat the pruritus of cholestasis by some clinicians (NVBergasa, personal conversations). The rationale to use steroids is not readily available; however, a steroid-response element [45] in the genes that concern detoxification pathways has been described. Accordingly, it seems plausible that the enhanced metabolism or detoxification of substances, including the pruritogen(s), may result in the relief of pruritus. Until some evidence supports this idea, the indiscriminate use of steroids to treat the pruritus of cholestasis is not recommended as side effects (e.g. infection, osteopenia) are a concern. In the context of immunosuppression, a recent case report has been published on the relief of pruritus in a patient with PBC associated with topical tacrolimus [125]. The mechanism behind this observation is a mystery at the time of this writing, as the skin of patients with the pruritus of cholestasis is devoid of primary pruritic skin lesions.

It seems appropriate to state at this point that relevant clinical observations would benefit from controlled pilot studies that apply objective methodology to diminish the large placebo effect present in all the studies of pruritus. If objective methodology is not available, a yes or no answer to the question of relief may be preferable to the use of vague questionnaires.

14. An approach to a patient with cholestasis and pruritus

Once it is determined that the pruritus is due to cholestasis (e.g. a diagnosis of liver disease has been established and other causes of pruritus have been excluded (e.g. skin conditions), the use of cholestyramine (Table) as the first type of drug seems reasonable as a prompt decision can be made regarding its effect. In the absence of response to cholestyramine or due to lack of tolerability, naltrexone proceeded by intravenous naloxone or not can be tried. If naltrexone treatment is not associated with a relief of pruritus, the clinician may choose to use sertraline, ondansetron, gabapentin or marinol in no particular order; all the options can be tried. In patients in whom the pruritus is not relieved by oral medications, intranasal butorphanol to a desirable maximum dose of 2 mg per day may also be tried. The use of rifampicin may be accompanied by liver toxicity; thus, its use in patients with this type of pruritus has to be considered in light of that risk. Combinations of the drugs listed above have been used without reported complications (NVBergasa, anecdotal reports, 2000–2004); however, careful follow up to identify potential side effects, in particular, psychiatric and neurological, is necessary. It is prudent to follow the liver profile of patients with cholestasis and pruritus in whom new medications are started to detect any signs of drug-induced liver injury, which would prompt discontinuation of the drug(s).

Invasive procedures, which include plasmapheresis, and MARS, and anesthesia with intravenous propofol may be saved for patients with intractable pruritus. Referral to liver transplantation may be reserved for patients who are refractory to conventional and experimental treatments. This precaution is particularly important, as pruritus can be intermittent, such as that seen in patients with benign recurrent intrahepatic cholestasis and even in chronic cholestasis. In this context, it should be noted that spontaneous remissions of pruritus in patients with advanced liver disease can be a predictor of liver failure [36].

The need to provide effective relief of the pruritus in patients with cholestasis highlights the importance of referring patients for participation in clinical trials. Studies in molecular pharmacology may provide insight into some reported antipruritic effects of compounds that, at present, escape a mechanistic definition.

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