

REVIEW ARTICLE

Drug-induced Pruritus: A Review

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Pruritus is an unpleasant sensation that leads to scratching. In addition to several diseases, the administration of drugs may induce pruritus. It is estimated that pruritus accounts for approximately 5% of all skin adverse reactions after drug intake. However, to date there has been no systematic review of the natural course and possible underlying mechanisms of drug-induced pruritus. For example, no clear distinction has been made between acute or chronic (lasting more than 6 weeks) forms of pruritus. This review presents a systematic categorization of the different forms of drug-induced pruritus, with special emphasis on a therapeutic approach to this side-effect. Key words: itch; pruritus; chronic; medication; side-effects.

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Pruritus is an unpleasant sensation that leads to intensive scratching (1). Chronic pruritus (lasting longer than 6 weeks) is the most common symptom in dermatology and can occur with or without visible skin lesions. Various skin and systemic diseases have been characterized to be associated with the presence of pruritus, and different mechanisms have been proposed to explain its origin (1, 2).

We present herein a detailed literature review in order to analyse the frequency and course of drug-induced pruritus, describe the most frequent drugs inducing acute and chronic pruritus, and present a new systematic categorization of the different forms of drug-induced pruritus, with special emphasis on a therapeutic approach to this side-effect.

GENERAL CONSIDERATIONS

The prevalence of drug-induced pruritus has not been studied well so far. In one large epidemiological study it has been shown that, among hospitalized patients, pruritus without concomitant skin lesions accounted for approximately 5% of adverse reactions after drug intake (3). However, these data are difficult to extra-

polate to drugs that are prescribed mainly in outpatient clinics, as only inpatients were analysed. In another study on skin reactions due to antibacterial agents used in 13,679 patients treated by general practitioners, cutaneous adverse effects were reported in 135 (1%) subjects, and general pruritus accounted for 13.3% of these reactions (4). In a recent analysis of 200 patients with drug reactions, 12.5% showed pruritus without skin lesions (5). However, only a few drugs have been analysed more carefully in relation to pruritus, mainly antimalarials, opioids, and hydroxyethyl starch (see below). Furthermore, analysing the available data on other drugs, it is sometimes very difficult to distinguish between “pure” drug-induced pruritus and symptomatic pruritus accompanying, for example, drug-induced urticaria or lichenoid eruptions (1, 6, 7).

The natural course of drug-induced pruritus depends on the drug applied and is not stereotypical. Drug-induced pruritus may be acute (lasting only several days) or chronic (longer duration for weeks or months). It may start with the first drug administration or may be delayed in time. For instance, in case of liver dysfunction, pruritus usually appears several weeks after the start of the treatment (8–11), although it was also reported after relatively short-term therapy periods (12). Drug-induced pruritus can be localized or generalized (1, 6, 13), and may resolve shortly after drug discontinuation (14) or may persist even for several months or years after treatment withdrawal (15–17).

The pathogenesis of drug-induced pruritus differs depending upon the causative agent. Pruritus may be secondary to drug-induced skin lesions, but a number of other possible mechanisms of drug-induced pruritus have been postulated, including cholestatic liver injury, xerosis of the skin, deposits of drugs or their metabolites in the skin, phototoxicity, or neurological alterations. Often, the underlying mechanism is not known (18).

CATEGORIES OF DRUG-INDUCED PRURITUS

Summarizing our literature research, for some drugs a clear time-relation has been described and interruption of the drug leads to cessation of pruritus. Pruritus usually lasts less than 6 weeks in this group, fulfilling the definition of acute pruritus. In other drugs, pruritus lasts much longer due to the underlying mechanisms. For example, in hydroxyethyl starch (HES)-induced

pruritus, neuronal storage of the substance evokes pruritus, which slowly relieves after degradation of the substance. This can be grouped as chronic pruritus, since it lasts for more than 6 weeks. In addition, many drugs are described to induce chronic pruritus by unknown mechanisms. In this group of drug-induced pruritus, therapy is very difficult, including the decision to interrupt or change the drug prescription. According to our experience, interruption for at least 6 weeks is necessary to prove that chronic pruritus is due to the accused drug. In sum, several groups of drug-induced pruritus can be defined, as summarized in Table I.

The most important groups of drugs that might be responsible for pruritus are listed in Table II. However, these data must be considered with some caution, as it is almost impossible to mention all drugs that could evoke itching. Pruritus is most often mentioned as a complication after systemic drugs. However, pruritus may also accompany local skin or mucous membrane reaction after topical application of different medicines, e.g. ciprofloxacin (132) or calcineurin inhibitors (133).

ACUTE PRURITUS

Pruritus induced by chloroquine and other antimalarials

Chloroquine, a widely used anti-malarial agent, may produce pruritus of unknown mechanism in up to 60–70% of Black Africans (61–64). This type of pruritus has been considered as severe in almost 60% of pruritic subjects (62–64). Interestingly, chloroquine-induced pruritus is uncommon in Caucasian or Asian people (65, 66). In the study by Bussaratid et al. (65) among Thailand's population only 1.9% of over 1000 malaria patients experienced pruritus due to chloroquine therapy. Regarding Black Africans, pruritus appeared mainly in young patients (<40 years of age) and the majority of patients experienced the onset of itching within the first 24 h after chloroquine ingestion (64). Pruritus lasted longer than 48 h after the last dose of chloroquine in nearly half of the patients (64). The longest duration for chloroquine-induced pruritus was 7 days (139). Chloroquine-induced pruritus may be limited to the hands and feet, while other subjects

may suffer from generalized itching (64, 65, 139). Chloroquine-induced pruritus is the most common adverse drug reaction experienced by Black Africans, and negatively affects compliance with antimalarial therapy (62). It has been shown that more than 10% of pregnant women avoided malaria chemoprophylaxis with chloroquine due to the fear of pruritus (67). Another study on antenatal patients documented that the frequency of pruritus with chloroquine was the only factor that correlated with the continuation of the use of this drug for malaria (140).

Pruritus was also reported after other antimalarials, such as amodiaquine, halofantrine and hydroxychloroquine, although less commonly and with lower intensity (68–71). Frequently, aquagenic or post-wetness type of pruritus without visible skin lesions was observed, usually located in the lower extremities and back (71). It appeared approximately 1–3 weeks after initiation of treatment and developed mainly after hot showers, beginning within minutes of water contact, persisting at a high intensity for several minutes, and then remaining at low intensity for several hours (71).

The pathogenesis of chloroquine-induced pruritus remains unclear. Genetic background seems to be a strong predisposing factor, as this symptom is observed mainly in Black Africans. Chloroquine has been shown to release histamine, and antihistamic drugs have been demonstrated to be effective in a subgroup of patients (61, 62, 72). Severity of pruritus also correlated with the antecedent malaria parasite density in the blood (61). Furthermore, there was a reduced frequency of the sickle cell trait among itchers relative to non-itchers, while glucose-6-phosphate dehydrogenase deficiency was more common among pruritics than non-pruritics (141). In addition, it was suggested that subjects with pruritus may present slower metabolism of chloroquine, leading to higher plasma concentrations of chloroquine, although the overall pharmacokinetic patterns were comparable in both pruritic and non-pruritic patients (73, 74). Another possibility is mediation of pruritus in malaria individuals by endogenous opioid peptides via μ -opioid receptors (62, 75). Based on these data, it seems that chloroquine-induced pruritus should be considered as a multifactorial phenomenon.

Table I. Drug-induced pruritus (without skin rash)

	Acute pruritus (<6 weeks duration)	Chronic pruritus (>6 weeks duration)
Characteristic	Spontaneous relief after interruption of drug	No spontaneous cessation after drug interruption Group I: Pathomechanism known. Clear time-relation between intake of a drug and onset of pruritus. Group II: No hypothesis of pathomechanisms. Late onset of pruritus.
Examples	Opioid-induced pruritus; in 60–90% of patients upon spinal administration (e.g. morphine, sufentanil, fentanyl, butorphanol). Starts 6–12 h after administration Chloroquine: 55–90% of patients (Black Africans) upon anti-malarial therapy. Itching for 1–3 days	Group I: Hydroxyethyl starch induced pruritus. Starts 3 weeks after infusion therapy with a dosage >200 g (60 g / 1 l). Generalized, severe, intractable pruritus with duration up to 15 months. Group II: e.g. Glimepiride: <1% of patients.

Table II. *Drugs that could induce pruritus*

Group of drugs	Examples	Possible mechanism of pruritus	Frequency of pruritus	Ref.
Antihypertensive drugs	Angiotensin-converting enzyme inhibitors	Increase of bradykinin level or cholestatic liver injury or secondary to skin lesions	1–15%	19–25
	Angiotensin II antagonists (sartans)	Cholestatic liver injury	Case reports	7, 26
	Beta-adrenergic blockers	Secondary to skin lesions	Frequent, if administered transdermally	27
		Cholestatic liver injury	Rare	28
	Calcium channel blockers	Secondary to skin lesions or unknown	<2%	13, 29, 30
		Cholestatic liver injury	Case reports	14, 31
	Methyldopa	Unknown or secondary to skin lesions	<2%	24, 32
	Sildenafil	Cholestatic liver injury	Case report	33
		Cholestatic liver injury	Case reports	34
Anti-arrhythmic drugs	Amiodarone	Cholestatic liver injury	Case reports	34
Anticoagulants	Ticlopidine	Cholestatic liver injury	Case reports	8
	Fractionated heparins	Urticarial reaction	Case reports	35
Anti-diabetic drugs	Biguanides	Cholestatic liver injury	Case reports	11
	Sulphonylurea derivatives	Unknown	<5%	36, 37
Hypolipaeic drugs	Statins	Unknown or secondary to skin lesions	16%	38–40
Antibiotics and chemotherapeutics	Penicillins	Secondary to skin lesions or cholestatic liver injury	2–20%	41, 42
	Cephalosporins	Unknown or secondary to skin lesions	<2%	43–45
	Macrolides	Secondary to skin lesions or cholestatic liver injury	<0.3%	4, 7
	Carbapenemes	Cholestatic liver injury	Rare	12, 46
	Monobactams	Secondary to skin lesions	Rare	47
	Quinolones	Unknown or secondary to skin lesions	1–4%	48–52
	Tetracyclines	Unknown or cholestatic liver injury	1–2%	9, 53, 54
	Lincosamides	Secondary to skin lesions or cholestatic liver injury	Rare	47, 55
	Streptogramins	Secondary to skin lesions	2.5%	56
	Metronidazole	Unknown or secondary to skin lesions	<5%	57
	Rifampin	Unknown	Case report	58
	Tiamphenicol	Unknown	<0.1%	59
	Trimethoprim/ sulphamethoxazole	Secondary to skin lesions	2–10%	4, 60
		Cholestatic liver injury	Rare	15
	Antimalarials	Unknown, but genetic background is important: release of histamine or activation of μ -receptors were postulated	Up to 60–70% of Black Africans, uncommon in Caucasians or Asians	61–76
		Cholestatic liver injury	Rare	16
Psychotropic drugs	Tricyclic antidepressants	Cholestatic liver injury	Rare	77, 78
	Selective serotonin re-uptake inhibitors	Activation of peripheral serotonin receptors or secondary to skin lesions	Rare	79–82
	Neuroleptics	Cholestatic liver injury	Rare	83–87
Anti-epileptics	Carbamazepine, fosphenytoin, oxcarbazepine, phenytoin, topiramate	Secondary to skin lesions, allergic reaction	Rare	88
Cytostatics	Chlorambucil	Secondary to skin lesions	Case reports	89–91
	Paclitaxel	Unknown or secondary to skin lesions	10–14%	92
	Tamoxifen	Sebstasis/xerosis	3–5%	93
Cytokines, growth factors and monoclonal antibodies	Granulocyte-macrophage colony-stimulating factor	Unknown	Common	94–96
	Interleukin 2	Direct pruritogenic effect of IL-2	Very common	91
	Matuzumab	Unknown	<10%	97
	Lapatinib	Unknown or urticarial reaction	3%	98–108
Plasma volume expanders	Hydroxyethyl starch (HES)	Deposition of HES in small peripheral nerves or in Schwann's cells of cutaneous nerves	12.6–54%	99–108
Others	Anti-thyroid agents	Cholestatic liver injury	Rare	10
	Non-steroidal anti-inflammatory drugs	Increased synthesis of leukotrienes	1–7%	109, 110
	Corticosteroids	Cholestatic liver injury	Rare	111
	Sex hormones	Cholestatic liver injury	Very rare	112
	Opioids	Centrally mediated process via μ -opioid receptor	Rare	113–115
	Inhibitors of xanthine oxidase	Centrally mediated process via μ -opioid receptor	2–100%	116–130
		Secondary to skin lesions	0.8–2.1%	131

Table III. Proposed treatment of drug-induced pruritus, especially if pruritus persists after interruption of drug intake

Type of pruritus	First-line treatment (ref)	Second-line treatment (ref)	Third-line treatment (ref)
Chloroquine-induced	Antihistaminics (promethazine, chlorpromazine) (62, 64, 65, 72)	μ -receptor antagonists (naltrexone) (62)	Prednisolone (61, 76) Niacin (61, 76)
Opioid-induced	Naloxone, naltrexone (μ -receptor antagonists) or nalbuphine (partial κ -receptor agonist, μ -receptor antagonists) – may reduce analgesia (134)	Dopamine (D_2) receptor antagonist (droperidol, alizapride) (134)	Serotonin (5-HT ₃) receptor antagonists (ondansetron, dolasetron) Sedating antihistaminics (promethazine, diphenhydramine) Cyclooxygenase-1 inhibitors (tenoxicam, diclofenac) – poorly documented efficacy
Hydroxyethyl starch-induced	μ -receptor antagonists (naltrexone) (135)	Phototherapy (136)	Topical capsaicin (136)
Pruritus secondary to cholestatic liver disease	Ursodeoxycholic acid or rifampicin (26, 137, 138)	Cholestyramine (26, 137, 138)	μ -receptor antagonists (naloxone, naltrexone) (26, 137, 138) Sertraline (138)
Other types of drug-induced pruritus	High doses of antihistaminics	μ -receptor antagonists	Gabapentin, paroxetine, amitriptyline (90)

The most commonly prescribed medications for chloroquine-induced pruritus are antihistaminics (64, 65) (Table III). However, they are only partially effective (72). Pruritus may also be reduced by concurrent administration of a single oral dose of prednisolone (10 mg) or niacin (50 mg) with no negative influence on malaria parasite clearance or clinical amelioration (61, 76). Another interesting therapeutic option is naltrexone, which exerted at least a similar antipruritic effect in patients with chloroquine-induced itch as observed in the group treated with promethazine (62).

Serotonin re-uptake inhibitors

Another group of drugs that may sometimes be responsible for itching is the serotonin re-uptake inhibitors (SRIs) (77, 78). Interestingly, these drugs are also used as effective antipruritic agents due to their activity on the central nervous system (142). However, in some patients SRIs may lead to increased peripheral concentrations of serotonin and thus induce itching in individuals who are sensitive to higher concentrations of serotonin. It was shown that intradermally injected serotonin may provoke itching in healthy subjects (143). Similarly, serotonin induced a dose-dependent increase of nasal itching after nasal challenge (144). Pruritus can appear in particular in those patients treated with SRIs who also consume products containing high amounts of serotonin, serotonin precursors or alkaloids capable of releasing serotonin, e.g. chocolate (77).

Opioid-induced pruritus

Opioids are frequently used for the treatment of acute and chronic pain. One of the common side-effects of opioid therapy is pruritus (116). A wide variety of opioids were identified as evoking itching (117–122). The incidence of pruritus depends on the opioid used and its mode of administration (116, 123). Pruritus is recognized in ap-

proximately 2–10% of patients treated orally with these drugs (116). The risk is increased when opioids are administered epidurally or intrathecally, and the highest incidence (up to 100%) is associated with intrathecal morphine (43, 123–125). Parturients appear to be the most susceptible group (124, 125). The incidence of itching also rises with increasing doses of opioids (125). Facial areas innervated by the trigeminal nerve are mostly affected, probably due to the high concentration of opioid receptors in the spinal nucleus of the trigeminal nerve. Typically, patients scratch the nose, perinasal area and upper part of the face, although generalized pruritus has also been reported (123, 124).

The postulated mechanism of opioid-induced pruritus is a centrally mediated process via μ -opioid receptors (126–129). Naloxone, a classic μ -receptor antagonist, was effective in preventing or treating intrathecal or epidural opioid-induced itching (130). Modulation by the serotonergic pathway and involvement of prostaglandins or histamine may also be important (124). In addition, stimulation of opioid receptors in the skin by opioids cannot be excluded (130). The medullary dorsal horn may be a critical site for the action of opioids in producing pruritus (127, 128). In monkeys, morphine injected unilaterally into this region causes ipsilateral facial scratching (127, 128).

Although opioid-induced pruritus is easy to treat, some problems still have to be resolved. Several treatment modalities have been tried, but no one was fully satisfactory (see Table III). Opioid antagonists may have a role in the prevention of opioid-induced pruritus; however, both naloxone and naltrexone decreased the analgesia, especially at higher doses (130, 145–148). Nalbuphine (a 40 mg intravenous bolus) also effectively prevented pruritus without increasing pain, but the treatment was associated with increased drowsiness (130). Moreover, nalbuphine was shown to be ineffective in the treatment of postoperative opioid-induced pruritus in paediatric patients (149). The usage of 5-HT₃ re-

ceptor antagonists (ondansetron, dolasetron) remains controversial. Some authors reported good efficacy (123, 141, 150–152) while others denied it (153–155). In addition, antihistaminics, droperidol, propofol, alizapride, tenoxicam and diclofenac have been tried with various success (116, 124, 141, 156). Recently, it has been shown that preoperative gabapentin prevents pruritus induced by intrathecal morphine in patients undergoing lower limb surgery with spinal anaesthesia (157). Another interesting option of pruritus prevention is the reduction in opioid dose by the combination of opioid with other drugs, e.g. sufentanil with bupivacaine (158). Such combination offers satisfactory analgesia with a very low incidence of pruritus (158).

CHRONIC PRURITUS

Pruritus induced by hydroxyethyl starch (HES)

HES is an artificial colloid commonly used for clinical fluid management (98). The usage of HES can be complicated by well defined side-effects, including coagulopathy, clinical bleeding, anaphylactoid reactions and pruritus (98). Because of the delayed onset of pruritus after HES administration, this symptom had not been recognized as an adverse reaction of HES until lately. First case reports were published in the early 1980s (99, 100), but this side-effect was not properly documented until the early 1990s (98, 101–104). The frequency of pruritus after HES administration varied from 12.6% to 54% depending on the population studied (102, 105–108).

Pruritus may appear after even small volumes of HES (e.g. 60 g), but it seems that the usage of higher cumulative doses is connected with higher frequency and more severe pruritus (105, 106, 108). The symptom appears usually as pruritic crisis, lasting from 2 min to one hour, and is triggered by friction, bathing in warm water or physical stress (17, 98, 108). Pruritus may be generalized or localized, involving any part of the body and there is no site predilection (98, 104, 108). As mentioned above, the onset of pruritus is delayed in time and usually starts within 3–6 weeks after HES infusion (98, 106). It is often very severe and may last for several weeks or even months. In the study of Kimme et al. (108) the median onset of pruritus after the administration of HES was 4 weeks and the median duration was 15 weeks. In another study, symptoms resolved spontaneously after the median period of 10 months, but in individual patients pruritus was observed for as long as 18–24 months (17). Because of the severity of pruritus and poor efficacy of the therapy (see below), patients with HES-induced pruritus often present with sleep disturbances and impaired quality of life (98, 105). Some patients may also need psychiatric support due to the anxiety. Suicide as a result of HES-induced pruritus has been reported (98).

The pathogenesis of pruritus induced by HES is still not fully clear, but it seems that it may be elucidated

by the neuronal storage of HES that leads to direct activation of pruritogenic nerves. Deposits of HES were found in cutaneous nerves (Schwann cells, perineuronal cells, endoneurial macrophages), dermal macrophages, endothelial cells of blood and lymph vessels, and in some keratinocytes and Langerhans' cells (17, 103, 104, 159). It was noted, that after high cumulative doses of HES, pruritus closely correlated with HES deposition in cutaneous nerves (17). Interestingly, HES deposits in nerves have persisted for no longer than 17 months, paralleling the cessation of pruritus (160). It has been suggested that HES deposits may mechanically irritate nerve endings, thus provoking pruritus (17, 98, 104). Whether other HES-containing cells also partake in provoking pruritus or exert a more direct effect on sensory nerves fibres remains unclear (98).

Treatment of HES-induced pruritus is very difficult, as most currently available antipruritic strategies are not effective (see Table III). No improvement was observed after antihistaminic drugs, the most widely used antipruritic agents (101–103, 108). Glucocorticoids, neuroleptics, oil baths or acetaminophen were also shown to be ineffective too (98). One study documented a good response to topical capsaicin, but this treatment regimen is frequently poorly tolerated due to burning sensations (136). Some patients may respond to oral naltrexone (135) and, finally, gradual relief has been reported over a period of several weeks with ultraviolet therapy in part of the studied population (136). However, no controlled studies have been performed to date assessing these treatment methods of HES-induced pruritus.

CONCLUSION

In summary, many drugs can be responsible for acute or chronic pruritus; however, drug-induced itching and the underlying mechanisms have not yet been studied in depth. Moreover, various mechanisms could be involved in the pathology of this symptom. Therefore, treatment options of drug-induced pruritus are very limited and new treatment modalities have to be sought. Further detailed studies on the frequency of drug-induced pruritus following the use of particular medications, as well as research on its pathomechanisms, are strongly required.

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