Acta Derm Venereol 2009; 89: 236–244

REVIEW ARTICLE

Drug-induced Pruritus: A Review

Adam REICH[1], Sonja STÄNDER[2] and Jacek C. SZEPIETOWSKI[1,3]
[1]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, [2]Clinical Neurodermatology, Department of Dermatology, University Hospital of Münster, Germany, and [3]Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland

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.***

(Accepted January 19, 2009.)

Acta Derm Venereol 2009; 89: 236–244.

Adam Reich, Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Ul. T. Chalubinskiego 1, PL-50-368 Wroclaw, Poland. E-mail: adi_medicalis@go2.pl

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 extrapolate 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
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 derivates	Unknown	<5%	36, 37
Hypolipaemic 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
Psychotropic drugs	Tricyclic antidepressants	Cholestatic liver injury	Rare	16
	Selective serotonin re-uptake inhibitors	Activation of peripheral serotonin receptors or secondary to skin lesions	Rare	77, 78
	Neuroleptics	Cholestatic liver injury	Rare	79–82
Anti-epileptics	Carbamazepine, fosphenytoin, oxcarbazepine, phenytoin, topiramate	Secondary to skin lesions, allergic reaction	Rare	83–87
Cytostatics	Chlorambucil	Secondary to skin lesions	Case reports	88
	Paclitaxel	Unknown or secondary to skin lesions	10–14%	89–91
	Tamoxifen	Sebostasis/xerosis	3–5%	92
Cytokines, growth factors and monoclonal antibodies	Granulocyte-macrophage colony-stimulating factor	Unknown	Common	93
	Interleukin 2	Direct pruritogenic effect of IL-2	Very common	94–96
	Matuzumab	Unknown	<10%	91
	Lapatinib	Unknown or urticarial reaction	3%	97
Plasma volume expanders	Hydroxyethyl starch (HES)	Deposition of HES in small peripheral nerves or in Schwann's cells of cutaneous nerves	12.6–54%	98–108
Others	Anti-thyroid agents	Cholestatic liver injury	Rare	10
	Non-steroidal anti-inflammatory drugs	Increased synthesis of leukotrienes	1–7%	109, 110
		Cholestatic liver injury	Rare	111
	Corticosteroids	Cholestatic liver injury	Very rare	112
	Sex hormones	Cholestatic liver injury	Rare	113–115
	Opioids	Centrally mediated process via μ-opioid receptor	2–100%	116–130
	Inhibitors of xanthine oxidase	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, chloropromazine) (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, amitryptiline (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 approximately 2–10% of patients treated orally with these drugs (116). The risk is increased when opioids are administered epidurally or intraspinally, 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 serotoninergic 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, endoneural 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 antihistamic 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.

The authors declare no conflict of interest.

REFERENCES

1. Ständer S, Streit M, Darsow U, Niemeier V, Vogelgsang M, Ständer H, et al. Diagnostisches und therapeutisches Vorgehen bei chronischem Pruritus. J Dtsch Dermatol Ges 2006; 4: 350–370.
2. Steinhoff M, Bienenstock J, Schmelz M, Maurer M, Wie E, Bíró T. Neurphysiological, neuroimmunological, and neuroendocrine basis of pruritus. J Invest Dermatol 2006; 126: 1705–1718.

3. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975–1982. J Am Med Assoc 1986; 256: 3358–3363.
4. van der Linden PD, van der Lei J, Vlug AE, Stricker BH. Skin reactions to antibacterial agents in general practice. J Clin Epidemiol 1998; 51: 703–708.
5. Raksha MP, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 2008; 74: 80
6. Shirin H, Schapiro JM, Arber N, Pinkhas J, Sidi Y, Salomon F. Erythromycin base-induced rash and liver function disturbances. Ann Pharmacother 1992; 26: 1522–1523.
7. Morton A, Muir J, Lim D. Rash and acute nephritic syndrome due to candesartan. BMJ 2004; 328: 25.
8. Amaro P, Nunes A, Maçôas F, Ministro P, Baranda J, Cipriano A, et al. Ticlopidine-induced prolonged cholestasis: a case report. Eur J Gastroenterol Hepatol 1999; 11: 673–676.
9. Hunt CM, Washington K. Tetracycline-induced bile duct paucity and prolonged cholestasis. Gastroenterology 1994; 107: 1844–1847.
10. Mikhail NE. Methimazole-induced cholestatic jaundice. South Med J 2004; 97: 178–182.
11. Nammour FE, Fayad NF, Peikin SR. Metformin-induced cholestatic hepatitis. Endocr Pract 2003; 9: 307–309.
12. Quattropani C, Schneider M, Helbling A, Zimmermann A, Krähenbühl S. Cholangiopathy after short-term administration of piperacillin and imipenem/cilastatin. Liver 2001; 21: 213–216.
13. Orme S, da Costa D. Generalized pruritus associated with amlodipine. Br Med J 1997; 315: 463.
14. Odeh M, Oliven A. Verapamil-associated liver injury. Harefuah 1998; 134: 36–37.
15. Kowdley KV, Keeffe EB, Fawaz KA. Prolonged cholestasis due to trimethoprim sulfamethoxazole. Gastroenterology 1992; 102: 2148–2150.
16. Larrey D, Amouyal G, Pessayre D, Degott C, Danne O, Machayekhi JP, et al. Amitriptyline-induced prolonged cholestasis. Gastroenterology 1988; 94: 200–203.
17. Metze D, Reimann S, Szépfalusi Z, Bohle B, Kraft D, Luger TA. Persistent pruritus after hydroxyethyl starch infusion therapy: a result of long-term storage in cutaneous nerves. Br J Dermatol 1997; 136: 553–559.
18. Weisshaar E. Evidence-based medicine and pruritus. (Abstr. OP4) Acta Derm Venereol 2007; 87: 462.
19. Gavras H. A multicenter trial of enalapril in the treatment of essential hypertension. Clin Ther 1986; 9: 24–38.
20. Mulinari R, Gavras I, Gavras H. Efficacy and tolerability of enalapril monotherapy in mild-to-moderate hypertension in older patients compared to younger patients. Clin Ther 1987; 9: 678–689.
21. Nunes AC, Amaro P, Maçôas F, Cipriano A, Martins I, Rosa A, et al. Fosinopril-induced prolonged cholestatic jaundice and pruritus: first case report. Eur J Gastroenterol Hepatol 2001; 13: 279–282.
22. Parker WA. Captopril-induced cholestatic jaundice. Drug Intell Clin Pharm 1984; 18: 234–235.
23. Steckelings UM, Artuc M, Wollschläger T, Wiehstutz S, Henz BM. Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. Acta Derm Venereol 2001; 81: 321–325.
24. Thestrup-Pedersen K. Adverse reactions in the skin from antihypertensive drugs. Dan Med Bull 1987; 34 Suppl 1: 3–5.
25. Thind GS. Angiotensin converting enzyme inhibitors: comparative structure, pharmacokinetics, and pharmacodynamics. Cardiovasc Drugs Ther 1990; 4: 199–206.
26. Chitturi S, Farrell GC. Drug-induced cholestasis. Semin Gastrointest Dis 2001; 12: 113–124.
27. Jeck T, Edmonds D, Mengden T, Schubert M, Renz I, Weisser B, et al. Betablocking drugs in essential hypertension: transdermal bupranolol compared with oral metoprolol. Int J Clin Pharmacol Res 1992; 12: 139–148.
28. Hagmeyer KO, Stein J. Hepatotoxicity associated with carvedilol. Ann Pharmacother 2001; 35: 1364–1366.
29. Bernink PJ, de Weerd P, Ten CF, Remme WJ, Barth J, Enthoven R, et al. An 8-week double-blind study of amlodipine and diltiazem in patients with stable exertional angina pectoris. J Cardiovasc Pharmacol 1991; 17 Suppl 1: S53–S56.
30. Gonzalo Garijo MA, Pérez Calderón R, de Argila Fernández-Durán D, Rangel-Mayoral JF. Cutaneous reactions due to diltiazem and cross reactivity with other calcium channel blockers. Allergol Immunopathol (Madr) 2005; 33: 238–240.
31. Burgunder JM, Abernethy DR, Lauterburg BH. Liver injury due to verapamil. Hepatogastroenterology 1988; 35: 169–170.
32. Haider Z, Bano KA. Experience with anti-hypertensive drug therapy in a hypertension Clinic – 1972–1983. A retrospective analysis. J Pak Med Assoc 1990; 40: 91–93.
33. Wolfhagen FH, Vermeulen HG, de Man RA, Lesterhuis W. Initially obscure hepatotoxicity attributed to sildenafil. Eur J Gastroenterol Hepatol 2008; 20: 710–712.
34. Salti Z, Cloche P, Weber P, Haussemand G, Vollmer F. A case of cholestatic hepatitis caused by amiodarone. Ann Cardiol Angiol (Paris) 1989; 38: 13–16.
35. MacLaughlin EJ, Fitzpatrick KT, Sbar E, Jewell C. Anaphylactoid reaction to enoxaparin in a patient with deep venous thrombosis. Pharmacotherapy 2002; 22: 1511–1515.
36. Kilo C, Dudley J, Kalb B. Evaluation of the efficacy and safety of Diamicron in non-insulin-dependent diabetic patients. Diabetes Res Clin Pract 1991; 14 Suppl 2: 79–82.
37. Stewart RD, Anderson DE. Glycodiazine in diabetes mellitus: a clinical trial. Br Med J 1965; 2: 682–684.
38. Kashyap ML, McGovern ME, Berra K, Guyton JR, Kwiterovich PO, Harper WL, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. Am J Cardiol 2002; 89: 672–678.
39. Sharma M, Sharma DR, Singh V, Panwar RB, Hira HS, Mohan B, et al. Evaluation of efficacy and safety of fixed dose lovastatin and niacin (ER) combination in asian Indian dyslipidemic patients: a multicentric study. Vasc Health Risk Manag 2006; 2: 87–93.
40. Stoebner PE, Michot C, Ligeron C Durand L, Meynadier J, Meunier L. Simvastatin-induced lichen planus pemphigoides. Ann Dermatol Venereol 2003; 130: 187–190.
41. Wendel GD Jr, Stark BJ, Jamison RB, Molina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med 1985; 312: 1229–1232.
42. Adcock BB, Rodman DP. Ampicillin-specific rashes. Arch Fam Med 1996; 5: 301–304.
43. Shimokata K, Suetsugu S, Umeda H, Inada S, Torikai K, Morishita M, et al. Evaluation of T-2588 in the treatment of respiratory tract infection. Jpn J Antibiot 1986; 39: 2897–2913.
44. Sonoda T, Matsuda M, Nakano E, Mizutani S, Iwao N, Miyoshi S, et al. Clinical evaluation of cefixime (CFIX) in the treatment of urinary tract infection. Hinyokika Kiyo 1989; 35: 1267–1275.
45. Theopold M, Benner U, Bauernfeind A. Effectiveness and tolerance of cefixime in bacterial infections in the ENT area. Infection 1990; 18 Suppl 3: S122–S124.
46. Soza A, Riquelme F, Alvarez M, Duarte I, Glasinovic JC, Arrese M. Hepatotoxicity by amoxicillin/clavulanic acid: case report. Rev Med Chil 1999; 127: 1487–1491.
47. Gonzalo-Garijo MA, de Argila D. Erythroderma due to

aztreonam and clindamycin. Investig Allergol Clin Immunol 2006; 16: 210–211.
48. Cook JA, Silverman MH, Schelling DJ, Nix DE, Schentag JJ, Brown RR, et al. Multiple-dose pharmacokinetics and safety of oral amifloxacin in healthy volunteers. Antimicrob Agents Chemother 1990; 34: 974–979.
49. Cox CE. A comparison of the safety and efficacy of lomefloxacin and ciprofloxacin in the treatment of complicated or recurrent urinary tract infections. Am J Med 1992; 92: 82S–86S.
50. Williams DJ, Hopkins S. Safety and tolerability of intravenous–to-oral treatment and single-dose intravenous or oral prophylaxis with trovafloxacin. Am J Surg 1998; Suppl 176: 74S–79S.
51. Ball P. Ciprofloxacin: an overview of adverse experiences. J Antimicrob Chemother 1986; 18 Suppl D: 187–193.
52. Hessen MT, Ingerman MJ, Kaufman DH, Weiner P, Santoro J, Korzeniowski OM, et al. Clinical efficacy of ciprofloxacin therapy for gram-negative bacillary osteomyelitis. Am J Med 1987; 82: 262–265.
53. Goulden V, Glass D, Cunliffe WJ. Safety of long-term high-dose minocycline in the treatment of acne. Br J Dermatol 1996; 134: 693–695.
54. Report to the Research Committee of the British Tuberculosis Association by the Clinical Trials Subcommittee. Comparison of side-effects of tetracycline and tetracycline plus nystatin. Br Med J 1968; 4: 11–15.
55. Aygun C, Kocaman O, Gurbuz Y, Senturk O, Hulagu S. Clindamycin-induced acute cholestatic hepatitis. World J Gastroenterol 2007; 13: 5408–5410.
56. Lamb HM, Figgitt DP, Faulds D. Quinupristin/dalfopristin: a review of its use in the management of serious gram-positive infections. Drugs 1999; 58: 1061–1097.
57. Kapoor K, Chandra M, Nag D Paliwal JK, Gupta RC, Saxena RC. Evaluation of metronidazole toxicity: a prospective study. Int J Clin Pharmacol Res 1999; 19: 83–88.
58. Walker-Renard P. Pruritus associated with intravenous rifampin. Ann Pharmacother 1995; 29: 267–268.
59. Siboulet A, Bohbot JM, Lhuillier N, Siboulet A, Catalan F. "One-minute treatment" with thiamphenicol in 50,000 cases of gonorrhea: a 22-year study. Sex Transm Dis 1984; 11 Suppl 4: 391–395.
60. Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus disease. Lancet 1991; 337: 468–471.
61. Adebayo RA, Sofowora GG, Onayemi O, Udoh SJ, Ajayi AA. Chloroquine-induced pruritus in malaria fever: contribution of malaria parasitaemia and the effects of prednisolone, niacin, and their combination, compared with antihistamine. Br J Clin Pharmacol 1997; 44: 157–161.
62. Ajayi AA, Kolawole BA, Udoh SJ. Endogenous opioids, μ-opiate receptors and chloroquine-induced pruritus: A double-blind comparison of naltrexone and promethazine in patients with malaria fever who have an established history of generalized chloroquine-induced itching. Int J Dermatol 2004; 43: 972–977.
63. Ekpechi OL, Okoro AN. A pattern of pruritus due to chloroquine. Arch Dermatol 1964; 89: 631–632.
64. Olayemi O, Fehintola FA, Osungbade A, Aimakhu CO, Udoh ES, Adeniji AR. Pattern of chloroquine-induced pruritus in antenatal patients at the University College Hospital, Ibadan. J Obstet Gynaecol 2003; 23: 490–495.
65. Bussaratid V, Walsh DS, Wilairatana P, Krudsood S, Silachamroon U, Looareesuwan S. Frequency of pruritus in Plasmodium vivax malaria patients treated with chloroquine in Thailand. Trop Doct 2000; 30: 211–214.
66. Spencer HC, Poulter NR, Lury JD, Poulter CJ. Chloroquine associated pruritus in a European. BMJ 1982; 285: 1703.
67. Kaseje DC, Sempebwa EK, Spencer HC. Malaria chemoprophylaxis to pregnant women provided by community health workers in Saradidi, Kenya. Reason for non-acceptance. Ann Trop Med Parasitol 1987; 81: 77–82.
68. Ezeamuzie IC, Igbigbi PS, Ambakederemo AW, Abila B, Nwaejike IN. Halofantrine-induced pruritus amongst subjects who itch to chloroquine. J Trop Med Hyg 1991; 94: 184–188.
69. Holme SA, Holmes SC. Hydroxychloroquine-induced pruritus. Acta Derm Venereol 1999; 79: 333.
70. Jiménez-Alonso J, Tercedor J, Jáimez L, García-Lora E. Antimalarial drug-induced aquagenic-type pruritus in patients with lupus. Arthritis Rheum 1998; 48: 744–745.
71. Jiménez-Alonso J, Tercedor J, Reche I. Antimalarial drugs and pruritus in patients with lupus erythematosus. Acta Derm Venereol 2000; 80: 458.
72. Osifo NG. The antipruritic effects of chlorpheniramine, cyproheptadine and sulphapyridine monitored with limb activity meters on chloroquine induced pruritus among patients with malaria. Afr J Med Med Sci 1995; 24: 67–73.
73. Ademowo OG, Sodeine O, Walker O. The disposition of chloroquine and its main metabolite desethylchloroquine in volunteers with and without chloroquine-induced pruritus: evidence for decreased chloroquine metabolism in volunteers with pruritus. Clin Pharmacol Ther 2000; 67: 237–241.
74. Onyeji CO, Ogunbona FA. Pharmacokinetic aspects of chloroquine-induced pruritus: influence of dose and evidence for varied extend of metabolism of the drug. Eur J Pharm Sci 2001; 13: 195–201.
75. Onigbogi O, Ajayi AA, Ukponmwan OE. Mechanism of chloroquine-induced body scratching behavior in rats: evidence of involvement of endogenous opioid peptides. Pharmacol Biochem Behav 2000; 65: 333–337.
76. Ajayi AA, Akinleye AO, Udoh SJ, Ajayi OO, Oyelese O, Ijaware CO. The effect of prednisolone and niacin on chloroquine-induced pruritus in malaria. Eur J Clin Pharmacol 1991; 41: 383–385.
77. Cederberg J, Knight S, Svenson S, Melhus H. Itch and skin rash from chocolate during fluoxetine and sertraline treatment: case report. B M C Psychiatry 2004; 4: 36.
78. Richard MA, Fiszenson F, Jreissati M, Jean Pastor MJ, Grob JJ. Cutaneous adverse effects during selective serotonin reuptake inhibitors therapy: 2 cases. Ann Dermatol Venereol 2001; 128: 759–761.
79. Chlumská A, Curík R, Boudová L, Mukensnabl P, Klvana P. Chlorpromazine-induced cholestatic liver disease with ductopenia. Cesk Patol 2001; 37: 118–122.
80. Moradpour D, Altorfer J, Flury R, Greminger P, Meyenberger C, Jost R, et al. Chlorpromazine-induced vanishing bile duct syndrome leading to biliary cirrhosis. Hepatology 1994; 20: 1437–1441.
81. Radzik J, Grotthus B, Leszek J. Disorder of liver functions in a schizophrenic patient after long-term risperidone treatment – case report. Psychiatr Pol 2005; 39: 309–313.
82. Regal RE, Billi JE, Glazer HM. Phenothiazine-induced cholestatic jaundice. Clin Pharm 1987; 6: 787–794.
83. Fischer JH, Patel TV, Fischer PA. Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. Clin Pharmacokinet 2003; 42: 33–58.
84. Knapp LE, Kugler AR. Clinical experience with fosphenytoin in adults: pharmacokinetics, safety, and efficacy. J Child Neurol 1998; 13 Suppl 1: S15–S18.
85. Ochoa JG. Pruritus, a rare but troublesome adverse reaction of topiramate. Seizure 2003; 12: 516–518.
86. Prosser TR, Lander RD. Phenytoin-induced hypersensitivity reactions. Clin Pharm 1987; 6: 728–734.
87. Wellington K, Goa KL. Oxcarbazepine: an update of its

efficacy in the management of epilepsy. C N S Drugs 2001; 15: 137–163.
88. Torricelli R, Kurer SB, Kroner T, Wüthrich B. Delayed allergic reaction to Chlorambucil (Leukeran). Case report and literature review. Schweiz Med Wochenschr 1995; 125: 1870–1873.
89. Dunphy FR, Boyd JH, Kim HJ, Dunphy CH, Harrison BR, Dunleavy TL, et al. A phase I report of paclitaxel dose escalation combined with a fixed dose of carboplatin in the treatment of head and neck carcinoma. Cancer 1997; 79: 2016–2023.
90. Freilich RJ, Seidman AD. Pruritis caused by 3-hour infusion of high-dose paclitaxel and improvement with tricyclic antidepressants. J Natl Cancer Inst 1995; 87: 933–934.
91. Kollmannsberger C, Schittenhelm M, Honecker F, Tillner J, Weber D, Oechsle K, et al. A phase I study of the humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody EMD 72000 (matuzumab) in combination with paclitaxel in patients with EGFR-positive advanced non-small-cell lung cancer (NSCLC). Ann Oncol 2006; 17: 1007–1013.
92. Love RR, Nguyen BD, Nguyen CB, Nguyen VD, Havighurst TC. Symptoms associated with oophorectomy and tamoxifen treatment for breast cancer in premenopausal Vietnamese women. Breast Cancer Res Treat 1999; 58: 281–286.
93. Hamm J, Schiller JH, Cuffie C, Oken M, Fisher RI, Shepherd F, et al. Dose-ranging study of recombinant human granulocyte-macrophage colony-stimulating factor in small-cell lung carcinoma. J Clin Oncol 1994; 12: 2667–2676.
94. Chi KH, Myers JN, Chow KC, Chan WK, Tsang YW, Chao Y, et al. Phase II trial of systemic recombinant interleukin-2 in the treatment of refractory nasopharyngeal carcinoma. Oncology 2001; 60: 110–115.
95. Gaspari AA, Lotze MT, Rosenberg SA, Stern JB, Katz SI. Dermatologic changes associated with interleukin 2 administration. J Am Med Assoc 1987; 258: 1624–1629.
96. Redman BG, Flaherty L, Chou TH, al-Katib A, Kraut M, Martino S, et al. A phase I trial of recombinant interleukin-2 combined with recombinant interferon-gamma in patients with cancer. J Clin Oncol 1990; 8: 1269–1276.
97. Lacouture ME, Laabs SM, Koehler M, Sweetman RW, Preston AJ, Di Leo A, et al. Analysis of dermatologic events in patients with cancer treated with lapatinib. Breast Cancer Res Treat 2009; 114: 485–493.
98. Bork K. Pruritus precipitated by hydroxyethyl starch: a review. Br J Dermatol 2005; 152: 3–12.
99. Bode U, Deisseroth AB. Donor toxicity in granulocyte collections: association of lichen planus with the use of hydroethyl starch leukapheresis. Transfusion 1981; 21: 83–85.
100. Parker NE, Porter JB, Williams HJ, Leftley N. Pruritus after administration of hetastarch. Br Med J (Clin Res Ed) 1982; 284: 385–386.
101. Schneeberger R, Albegger K, Oberascher G, Miller K. Pruritus – a side effect of hydroxyethyl starch? First report. HNO 1990; 38: 298–303.
102. Albegger K, Schneeberger R, Franke V, Oberascher G, Miller K. Itching following therapy with hydroxyethyl starch (HES) in otoneurological diseases. Wien Med Wochenschr 1992; 142: 1–7.
103. Jurecka W, Szépfalusi Z, Parth E, Schimetta W, Gebhart W, Scheiner O, et al. Hydroxyethylstarch deposits in human skin – a model for pruritus? Arch Dermatol Res 1993; 285: 13–19.
104. Gall H, Schultz KD, Boehncke WH, Kaufmann R. Clinical and pathophysiological aspects of hydroxyethyl starch-induced pruritus: evaluation of 96 cases. Dermatology 1996; 192: 222–226.
105. Sharland C, Hugett A, Nielson MS, Friedmann PS. Persistent pruritus after pentastarch infusions in intensive care patients. Anaesthesia 1999; 54: 500–501.
106. Morgan PW, Berridge JC. Giving long-persistent starch as volume replacement can cause pruritus after cardiac surgery. Br J Anaesth 2000; 85: 696–699.
107. Murphy M, Carmichael AJ, Lawler PG, White M, Cox NH. The incidence of hydroxyethyl starch-associated pruritus. Br J Dermatol 2001; 144: 973–976.
108. Kimme P, Jannsen B, Ledin T, Gupta A, Vegfors M. High incidence of pruritus after large doses of hydroxyethyl starch (HES) infusions. Acta Anaesthesiol Scand 2001; 45: 686–689.
109. Roll A, Wüthrich B, Schmid-Grendelmeier P, Hofbauer G, Ballmer-Weber BK. Tolerance to celecoxib in patients with a history of adverse reactions to nonsteroidal anti-inflammatory drugs. Swiss Med Wkly 2006; 136: 684–690.
110. Thumb N, Kolarz G, Scherak O, Mayrhofer F. The efficacy and safety of fentiazac and diclofenac sodium in peri-arthritis of the shoulder: a multi-centre, double-blind comparison. J Int Med Res 1987; 15: 327–334.
111. Chamouard P, Walter P, Baumann R, Paupon R. Prolonged cholestasis associated with short-term use of celecoxib. Gastroenterol Clin Biol 2005; 29: 1286–1288.
112. Topal F, Ozaslan E, Akbulut S, Küçükazman M, Yüksel O, Altiparmak E. Methylprednisolone-induced toxic hepatitis. Ann Pharmacother 2006; 40: 1868–1871.
113. Lieberman DA, Keeffe EB, Stenzel P. Severe and prolonged oral contraceptive jaundice. J Clin Gastroenterol 1984; 6: 145–148.
114. Medline A, Ptak T, Gryfe A, Blenkinsop B. Pruritus of pregnancy and jaundice induced by oral contraceptives. Am J Gastroenterol 1976; 65: 156–159.
115. Velayudham LS, Farrell GC. Drug-induced cholestasis. Expert Opin Drug Saf 2003; 2: 287–304.
116. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Pham Phys 2006; 74: 1347–1354.
117. Chamberlin KW, Cottle M, Neville R, Tan J. Oral oxymorphone for pain management. Ann Pharmacother 2007; 41: 1144–1152.
118. de Beer Jde V, Winemaker MJ, Donnelly GA, Miceli PC, Reiz JL, Harsanyi Z, et al. Efficacy and safety of controlled-release oxycodone and standard therapies for postoperative pain after knee or hip replacement. Can J Surg 2005; 48: 277–283.
119. Hadi MA, Kamaruljan HS, Saedah A, Abdullah NM. A comparative study of intravenous patient-controlled analgesia morphine and tramadol in patients undergoing major operation. Med J Malaysia 2006; 61: 570–576.
120. Jacobson L, Chabal C, Brody MC, Ward RJ, Wasse L. Intrathecal methadone: a dose-response study and comparison with intrathecal morphine 0.5 mg. Pain 1990; 43: 141–148.
121. Lane S, Evans P, Arfeen Z, Misra U. A comparison of intrathecal fentanyl and diamorphine as adjuncts in spinal anaesthesia for Caesarean section. Anaesthesia 2005; 60: 453–457.
122. Möhrenschlager M, Glöckner A, Jessberger B, Worret WI, Ollert M, Rakoski J, et al. Codeine caused pruritic scarlatiniform exanthemata: patch test negative but positive to oral provocation test. Br J Dermatol 2000; 143: 663–664.
123. Kyriakides K, Hussain SK, Hobbs GJ. Management of opioid-induced pruritus: a role for 5-HT3 antagonists? Br J Anaesth 1999; 82: 439–441.
124. Szarvas S, Harmon D, Murphy D. Neuraxial opioid-induced pruritus: a review. J Clin Anesth 2003; 15: 234–239.
125. Herman NL, Choi KC, Affleck PJ, Calicott R, Brackin R, Singhal A, et al. Analgesia, pruritus, and ventilation exhibit a dose-response relationship in parturients receiving intrathecal

fentanyl during labor. Analg Anesth 1999; 89: 378–383.
126. Ko MC, Song MS, Edwards T, Lee H, Naughton NN. The role of central μ opioid receptors in opioid-induced itch in primates. J Pharmacol Exp Ther 2004; 310: 169–176.
127. Thomas DA, Hammond DL. Microinjection of morphine into the rat medullary dorsal horn produces a dose-dependent increase in facial scratching. Brain Res 1995; 695: 267–270.
128. Thomas DA, Williams GM, Iwata K, Kenshalo DR Jr, Dubner R. The medullary dorsal horn. A site of action of morphine in producing facial scratching in monkeys. Anesthesiology 1993; 79: 548–554.
129. Tohda C, Yamaguchi T, Kuraishi Y. Intracisternal injection of opioids induces itch-associated response through μ-opioid receptor in mice. Jpn J Pharmacol 1997; 74: 77–82.
130. Waxler B, Dadabhoy ZP, Stojiljkovic L, Rabito SF. Primer of postoperative pruritus for anesthesiologists. Anesthesiology 2005; 103: 168–178.
131. Fitzgerald DA, Heagerty AH, Stephens M, Smith AG. Follicular toxic pustuloderma associated with allopurinol. Clin Exp Dermatol 1994; 19: 243–245.
132. Miró N. Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymyxin B, neomycin, and hydrocortisone suspension. Otolaryngol Head Neck Surg 2000; 123: 617–623.
133. Szepietowski J, Reich A, Białynicki-Birula R. Itching in atopic dermatitis: clinical manifestation, pathogenesis and the role of pimecrolimus in itch reduction. Dermatol Klin 2004; 6: 173–176.
134. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. Eur J Anaesthesiol 2001; 18: 346–357.
135. Metze D, Reimann S, Beissert S, Luger T. Efficacy and safety of neltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. J Am Acad Dermatol 1999; 41: 533–539.
136. Szeimies RM, Stolz W, Wlotzke U, Korting HC, Landthaler M. Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. Br J Dermatol 1994; 131: 380–382.
137. Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, Zylicz Z. Itch: scratching more than the surface. QJM 2003; 96: 7–26.
138. Kremer AE, Beuers U, Oude-Elferink RPJ, Pusl T. Pathogenesis and treatment of pruritus in cholestasis. Drugs 2008; 68: 2163–2182.
139. George AO. Chloroquine induced pruritus – questionnaire based epidemiological study. Afr J Health Sci 2004; 11: 87–92.
140. Olayemi O, Fehintola FA, Osungbade A, Aimakhu CO, Udoh ES, Adeniji AR. Pattern of chloroquine-induced pruritus in antenatal patients at the University College Hospital, Ibadan. J Obstet Gynaecol. 2003; 23: 490–495.
141. Ademowo OG, Sodeinde O. Certain red cell genetic factors and prevalence of chloroquine-induced pruritus. Afr J Med Med Sci 2002; 31: 341–343.
142. Ständer S, Böckenholt B, Schürmeyer-Horst F, Weishaupt C, Heuft G, Luger TA, et al. Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. Acta Derm Venereol 2009; 89: 45–51.
143. Weisshaar E, Ziethen B, Gollnick H. Can a serotonin type 3 (5-HT3) receptor antagonist reduce experimentally-induced itch? Inflamm Res 1997; 46: 412–416.
144. Tonnesen P, Schaffalitzky de Muckadell OB, Mygind N. Nasal challenge with serotonin in asymptomatic hay fever patients. Allergy 1987; 42: 447–450.
145. Charuluxananan S, Kyokong O, Somboonviboon W, Lertmaharit S, Ngamprasertwong P, Nimcharoendee K. Nalbuphine versus propofol for treatment of intrathecal morphine-induced pruritus after cesarean delivery. Anesth Analg 2001; 93: 162–165.
146. Charuluxananan S, Kyokong O, Somboonviboon W, Narasethakamol A, Promlok P. Nalbuphine versus ondansetron for prevention of intrathecal morphine-induced pruritus after cesarean delivery. Anesth Analg 2003; 96: 1789–1793.
147. Kendrick WD, Woods AM, Daly MY, Birch RF, DiFazio C. Naloxone versus nalbuphine infusion for prophylaxis of epidural morphine-induced pruritus. Anesth Analg 1996; 82: 641–647.
148. Okutomi T, Saito M, Mochizuki J, Amano K. Prophylactic epidural naloxone reduces the incidence and severity of neuraxial fentanyl-induced pruritus during labour analgesia in primiparous parturients. Can J Anesth 2003; 50: 961–962.
149. Nakatsuka N, Minogue SC, Lim J, Montgomery CJ, Court CA, Malherbe S, Csanyi-Fritz Y, et al. Intravenous nalbuphine 50 microg x 1 kg(-1) is ineffective for opioid-induced pruritus in pediatrics. Can J Anaesth 2006; 53: 1103–1110.
150. Han DW, Hong SW, Kwon JY, Lee JW, Kim KJ. Epidural ondansetron is more effective to prevent postoperative pruritus and nausea than intravenous ondansetron in elective cesarean delivery. Acta Obstet Gynecol Scand 2007; 86: 683–687.
151. Iatrou CA, Dragoumanis CK, Vogiatzaki TD, Vretzakis GI, Simopoulos CE, Dimitriou VK. Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritus: a randomized, double-blind, placebo-controlled study. Anesth Analg 2005; 101: 1516–1520.
152. Larijani GE, Goldberg ME, Rogers KH. Treatment of opioid-induced pruritus with ondansetron: report of four patients. Pharmacotherapy 1996; 16: 958–960.
153. Korhonen AM, Valanne JV, Jokela RM, Ravaska P, Kortilla K. Ondansetron does not prevent pruritus induced by low-dose intrathecal fentanyl. Acta Anaesthesiol Scand 2003; 47: 1292–1297.
154. Waxler B, Mondragon SA, Patel S, Nedumgottil K. Prophylactic ondansetron does not reduce the incidence of itching induced by intrathecal sufentanil. Can J Anesth 2004; 51: 685–689.
155. Wells J, Paech MJ, Evans SF. Intrathecal fentanyl-induced pruritus during labour: the effect of prophylactic ondansetron. Int J Obstet Anesth 2004; 13: 35–39.
156. Horta ML, Morejon LC, da Cruz AW, Dos Santos GR, Welling LC, Terhorst L, et al. Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. Br J Anaesth 2006; 96: 796–800.
157. Sheen MJ, Ho ST, Lee CH, Tsung YC, Chang FL. Preoperative gabapentin prevents intrathecal morphine-induced pruritus after orthopedic surgery. Anesth Analg 2008; 106: 1868–1872.
158. Demiraran Y, Ozdemir I, Kocaman B, Yucel O. Intrathecal sufentanil (1.5 μg) added to hyperbaric bupivacaine (0.5%) for elective cesarean section provides adequate analgesia without need for pruritus therapy. J Anaest 2006; 20: 274–278.
159. Reimann S, Szépfalusi Z, Kraft D, Luger T, Metze D. Hydroxyethyl starch accumulation in the skin with special reference to hydroxyethyl starch-associated pruritus. Dtsch Med Wochenschr 2000; 125: 280–285.
160. Ständer S, Szápfalusi Z, Bohle B, Ständer H, Kraft D, Luger TA, Metze D. Differential storage of hydroxyethyl starch (HES) in the skin: an immunoelectron-microscopical long-term study. Cell Tissue Res 2001; 304: 261–269.