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Drug-Induced Bladder and Urinary Disorders

Incidence, Prevention and Management

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Contents

Abstract

The bladder is vulnerable to the adverse effects of drugs because of its complex control and the frequent excretion of drug metabolites in the urine.

Incontinence results when bladder pressure exceeds sphincter resistance. Stress incontinence because of sphincter weakness occurs with antipsychotics and α-blockers, especially in women. Urge incontinence and irritive symptoms

may be caused by drugs. Anticholinergics, anaesthetics and analgesics cause urinary retention because of failure of bladder contraction. They are more likely to cause retention in men because of prostatic enlargement.

Cyclophosphamide and tiaprofenic acid can cause chemical cystitis, and should be withdrawn if a patient develops irritative symptoms or haematuria. Cyclophosphamide may also induce bladder tumours. Adverse effects of cyclophosphamide can be reduced with prophylactic administration of mesna and adequate hydration. Mitomycin, doxorubicin or bacillus Calmette-Guerin (BCG) instilled locally to treat bladder tumours can cause cystitis, contracture and calcification. Their administration should be limited to 1 hour per week for a maximum of 8 weeks. Retroperitoneal fibrosis and urine discolouration may be caused by drugs. Ureteric calculi may result from any drug causing nephrolithiasis.

Drugs and their metabolites are frequently excreted in the urine and this makes the lower urinary tract vulnerable to unwanted effects. The storage of urine means that carcinogens or inflammatory agents are in close proximity to the epithelium of the bladder for prolonged periods. The complexity of control and the diversity of pharmacological receptors present means that many drugs interfere with the storage and expulsion functions of the bladder, potentially resulting in incontinence or retention.

Prevention of drug-induced bladder or urinary disorders is difficult as most cases are idiosyncratic. However, populations at risk can be identified and drugs should be used with caution in these people, with careful follow up and due consideration of the possibility of bladder problems. Should a problem arise, management consists of the institution of supportive measures and withdrawal of the drug, which usually leads to resolution of the problem. Specific prevention and management problems are discussed in the relevant sections of this article. Incidence figures are provided where known, but in most instances they are either not known or may not reflect the true incidence.

This article reviews the literature covering adverse effects of drugs on the lower urinary tract. References were located by MEDLINE search and were supplemented from reference lists of key urological and pharmacological texts.

1. Urinary Incontinence

The storage of urine depends on low pressure filling with a competent sphincter mechanism, so that pressure within the bladder is less than the resistance of the sphincter and urethra. The entire urinary sphincter mechanism receives an important supply from the sympathetic nervous system, mediated by α-adrenoceptors. A defect in any aspect of this system may result in involuntary loss of urine.

1.1 Stress Incontinence

Sphincter weakness results in urine loss when intra-abdominal pressure is raised, as occurs on lifting and coughing. It is more common in women because of a lower urethral resistance, but can occur in men, particularly following prostatic surgery. It becomes more manifest with increasing age because of a general weakening of the musculature, which leads to increased urethral mobility and consequent sphincter dysfunction.

1.1.1 Antipsychotics

The major tranquillisers are dopamine antagonists with widespread actions. The mechanism by which they cause stress incontinence is unclear; inhibition of α-adrenoceptors or a centrally-mediated effect has been suggested.[1] Stress incontinence in women has been reported with thioridazine,[2] clozapine,[3] thiohexane, chlorpromazine and haloperidol.

To reduce the risk of incontinence it is important to use the lowest effective dosage, select agents with weak effect on α-adrenoceptors and consider adding anticholinergic agents.[3] Care is especially necessary in the elderly.

Symptoms usually resolve on discontinuation of the drug. Ephedrine has successfully been used to treat clozapine-induced incontinence.[3]

1.1.2 α-Blockers

In one study, 20 of 49 women patients (40.8%) taking α-blockers (prazosin, terazosin and doxazosin) were found to have urinary incontinence. Withdrawal of the drug in 17 of these patients reduced the number who were incontinent to 6 (14.0%), suggesting a causal effect.[4] The study did not specify the type of incontinence or which agents were more responsible. In a subsequent report, the same authors assessed the confounding variables in these patients and found an association between α-blockers, loop diuretics and chronic chest disease, all of which can exacerbate stress incontinence.[5] Allowing for these factors, the relative risk of urinary incontinence with α-blockers inhibitors fell to 1.96. Phentolamine[6] and prazosin[7] have been shown to reduce external sphincter function on urodynamic testing.

1.1.3 Other Drugs

A link between diuretics and/or conditions associated with their use and urinary incontinence has been reported.[8] Reserpine[1] and misoprostol[9] have been reported to cause stress incontinence. Enalapril was responsible for chronic dry cough and stress incontinence in a woman with a cystocoele; the cough and the incontinence ceased within 3 weeks of stopping the drug.[10] Urapidil resulted in enuresis in 2 elderly women patients, perhaps caused by α-adrenoceptor inhibition,[11] but the affinity of urapidil for serotonin 5-HT_{1A} receptors may also be relevant.[12] Previous use of oral contraception does not influence rates of incontinence.[13]

1.2 Urge Incontinence

Uninhibitable bladder contractions can overcome sphincter resistance, leading to urgency and incontinence. This has been described with colchicine[14] and diuretics.[8] Similar symptoms can occur from irritative lesions; a bladder stone containing the fluoroquinolone antibacterial tosufloxacin causing incontinence has been described.[15]

1.3 Overflow Incontinence

Overdistension of the bladder resulting from chronic urinary retention causes a rise in intravesical pressure and a resultant trickling loss of urine. Any drug causing urinary retention can thereby cause overflow incontinence; these are discussed in section 2.

2. Urinary Retention

Expulsion of urine involves bladder contraction, which requires cholinergic parasympathetic innervation, co-ordinated with sphincter relaxation, as occurs on reduction of the α-adrenoceptor input from the sympathetic nervous system. The co-ordination of the 2 components is integrated in the CNS. When expulsion fails, urine accumulates. Acute urinary retention is painful, often presenting as an emergency. A more insidious onset can lead to painless chronic retention which may lead to renal failure as a result of increased upper urinary tract pressure.

Predisposing factors for urinary retention include bladder outflow obstruction, neurogenic bladder dysfunction, urinary tract infection, acute pain, an unfamiliar environment, constipation and recumbency. Several of these factors may be involved in the development of post-operative urinary retention.

2.1 Anticholinergic Drugs

All drugs with antimuscarinic effects can cause or exacerbate urinary retention as a result of failure of bladder contraction, especially where there is pre-existing bladder outflow obstruction (table I).

Table I. Drugs with antimuscarinic effects, which may cause urinary retention or increased post-micturition residual volume

Tricyclic antidepressants
Amitriptyline
Imipramine
Clomipramine
Nortriptyline
Antispasmodics
Dicyclomine
Propantheline
Oxybutinin
Flavoxate
Mydriatic eyedrops
Atropine
Cyclopentolate
Antiparkinsonian agents
Benzhexol
Benzatropine (benztropine)
Orphenadrine
Procyclidine
Premedication
Atropine
Hyoscine
Glycopyrronium
Phenothiazine antipsychotics
Marked effect
Thioridazine
Moderate effect
Chlorpromazine
Methotrimeprazine
Promazine
Bronchodilators
Ipratropium bromide
Oxitropium bromide

Antispasmodics and tricyclic antidepressants may be used therapeutically for symptoms of urinary urgency, but they may cause retention where used inappropriately in patients with detrusor instability secondary to bladder outflow obstruction. Inhalation of nebulised ipratropium bromide for bronchodilation can cause retention, even though less than 1% of the drug is absorbed systemically.[16] The use of atropine during anaesthesia increases post-operative retention significantly.[17]

2.2 Anaesthesia and Analgesia

Post-operative retention occurs in 6 to 50% of patients with no prior urinary symptoms,[17,18] although the figure may be higher in patients with pre-existing urinary symptoms. The use of opioids for post-operative pain relief is associated with urinary retention when given by intravenous infusion,[17] intermittent intramuscular administration,[18] patient controlled analgesia systems,[19] extra-durally[20,21] and intrathecally.[20] In each study, the difficulty of controlling for confounding variables is clear. One study assessed urodynamic factors following administration of morphine, finding detrusor relaxation and corresponding voiding difficulties with the epidural route, but not with intramuscular or intravenous administration. This effect could be prevented with a single dose of naloxone.[22] Pethidine (meperidine), pentazocine, phenazocine, fentanyl and dipipanone have all been reported as causing urinary retention or difficulty in micturition. The mechanism by which opioids cause retention is unclear. Opioids have diverse effects on smooth muscle, which can be idiosyncratic. The effect may be centrally mediated, rather than local, through inhibition of the spinal micturition reflex, or it may simply be a problem of reduced awareness of bladder sensation.

General anaesthetic of duration greater than 60 minutes is a risk factor for post-operative urinary retention.[17] For spinal anaesthetics, the long-lasting local anaesthetic bupivacaine produced a higher incidence of urinary retention than short-acting lidocaine.[23] It was subsequently noted that this study failed to provide details of the baricity (osmotic concentration) of the agents used, which could have been relevant.[24]

Post-operative retention will usually resolve once anaesthetic and analgesic agents are fully cleared. It should, therefore, be possible to attempt a trial to check that they can pass urine without a catheter once the patient is fully mobile and any constipation or urinary tract infection is treated. Initial failure to void merits a longer recovery period. If further trial without a catheter is unsuccessful at 2 weeks, urological review will be necessary.

Naloxone has been used to treat post-operative urinary retention associated with opioids.[25] Urecholine prophylaxis was found not to affect catheterisation rates after anorectal surgery.[26]

2.3 Other Drugs

Antihistamines, especially the older agents, may have additional antimuscarinic effects. Their use should be avoided with other antimuscarinic drugs. Monoamine oxidase inhibitors may potentiate the adverse effects of any agent with antimuscarinic effects. Of the newer antihistamine agents, cetirizine, loratadine and terfenadine are said to have a low incidence of antimuscarinic effects, but there have been reports of retention associated with astemizole.[27] Prospective series, employing small numbers of patients, have failed to demonstrate significant decline in urodynamic parameters for terfenadine[28] and chlorpheniramine.[29]

α-Adrenoceptor agonists may contract the bladder neck, potentially resulting in increased obstruction sufficient to cause retention in men with prostatic hypertrophy.

There are reports of retention or difficulty with micturition with the following drugs; amphotericin B, chlormezanone, chlorphentermine, hydrallazine, leuprorelin (leuprolide),[30] metoclopramide,[31] nefopam,[32] phendimetrazine, phenelzine, phenytoin,[33] vinblastine and vincristine. Urinary retention has been described in a patient treated with clozapine and meclizine.[34] Use of large amounts of intravenous fluid peri-operatively may be a risk factor for post-operative retention.[23]

3. Cystitis

Cystitis is a descriptive term for irritative conditions affecting the bladder, regardless of aetiology, giving rise to symptoms of frequency, urgency and dysuria, with or without haematuria ('haemorrhagic' cystitis).

3.1 Cyclophosphamide

Cyclophosphamide is known to cause haemorrhagic and nonhaemorrhagic cystitis in patients being treated for neoplastic and non-neoplastic disease.[35-40] The incidence of cyclophosphamide induced haemorrhagic cystitis has been reported to be 2 to 40%,[36] but may be higher if cyclophosphamide is given concurrently with radiation therapy. The minimum total oral dose of cyclophosphamide that causes cystitis in adults is reported to be between 57 and 100g.[38,39] However, a lower dose may cause cystitis if the drug is given intravenously or to paediatric patients.[38] Acrolein, a metabolite of cyclophosphamide, is responsible for the urotoxicity.[41]

Adequate hydration is usually sufficient to prevent cystitis for patients receiving oral cyclophosphamide. It may also be sufficient, with or without a diuretic, for patients receiving the drug intravenously.[42] Overhydration must be avoided as cyclophosphamide can affect renal tubule function, resulting in inappropriate water retention.[43] Mesna (sodium 2-mercaptoethane-sulphonate) provides effective prophylaxis against cyclophosphamide cystitis.[44] It acts by binding acrolein in the bladder and also reduces the release of acrolein from its parent compound. It can be administered orally or intravenously and is usually given as a percentage of the cyclophosphamide dose (120% for oral, 60% for intravenous), in divided doses, before and after intravenous cyclophosphamide. Acetylcysteine binds acrolein and has been used as a bladder instillation, but this route fails to protect the upper urinary tract.[43]

Treatment of mild cyclophosphamide cystitis requires withdrawal of the drug and adequate hydration. Alkalising agents such as potassium citrate mixture should not be used, as a basic environment enhances release of acrolein.[45] Various agents have been used to treat severe haemorrhagic cystitis (table II) with varying degrees of success. They have been reviewed by Miller et al.[46]

Table II. Drugs used for treatment of severe haemorrhagic cystitis

Intravesical
Alum[36,46]
Carboprost[46,47]
Formalin[36,46,48]
Prostaglandin $F_{2\alpha}$[49]
Silver nitrate[36,46,48]
Intravenous
Conjugated estrogen[50]
Tranexamic acid[46]
Other
Hyperbaric oxygen[51]

3.2 Tiaprofenic Acid

Tiaprofenic acid is a nonsteroidal anti-inflammatory drug indicated for rheumatic diseases and musculoskeletal disorders. It acts by inhibiting prostaglandin synthesis. Cystitis associated with tiaprofenic acid has been well documented[52-54] but the mechanism by which this occurs is not known. It may be caused by a direct toxic effect, as 90% of the drug is excreted unchanged in the urine, but an immunological response has been postulated.[55]

Since 1984, the UK Committee on Safety of Medicines (CSM) has received 69 reports of cystitis associated with tiaprofenic acid and a further 32 reports of irritative urinary symptoms (frequency, dysuria and haematuria).[53] A recent survey of British and Irish urologists reported 108 cases, although the true figure may be greater, since only 47% of the urologists responded.[56] The association between tiaprofenic acid and cystitis has also been highlighted in Australia.[57]

Duration of treatment before the onset of symptoms of cystitis varies from days to years. Symptoms usually resolve within weeks of discontinuing the drug, although permanent changes, including ureteric obstruction,[58] have been reported.

Any patient developing urinary symptoms whilst taking tiaprofenic acid should discontinue the drug. The serious adverse effects of tiaprofenic acid in the absence of significant benefits over related drugs have cast doubts over the suitability of its continued use.[59] However, urinary tract symptoms have been attributed to other drugs in this group, making cystitis an adverse effect applicable to other nonsteroidal anti-inflammatory drugs.[60]

3.3 Other Drugs

Danazol, a semi-synthetic anabolic steroid, has been reported to cause haemorrhagic cystitis in patients with hereditary angioneurotic oedema.[61] In a series of 69 patients, 13 developed haematuria and 10 of these subsequently developed haemorrhagic cystitis. Tranilast (*N*-3′,4′-dimethoxycinnamoyl) anthranilic acid, an antiallergy preparation, may cause eosinophilic cystitis.[62] There have been 2 reports of allopurinol causing cystitis, but association may be coincidental as it is a rare complication for a widely used drug.[63] Carbenicillin may cause haemorrhagic cystitis.[64]

4. Induction of Bladder Cancer

4.1 Cyclophosphamide

Atypical urinary cytology in patients treated for lymphoma with cyclophosphamide was reported in 1964[65] and 2 cases of transitional cell carcinoma (TCC) were reported in 1971.[66] Several further cases followed.[67-69] The tumours tended to be of high grade with a poor prognosis. Leiomyosarcoma,[70] fibrosarcoma, spindle cell carcinoma[71] and squamous cell carcinoma[72] of the bladder have also been reported. The risk of TCC is comparatively small, but is hard to quantify because of confounding factors (smoking and occupational carcinogens, the long latency between exposure to cyclophosphamide and development of TCC, and the increased risk of second cancers in people with previous malignancy). An incidence of TCC of 1.8% has been reported for patients receiving cyclophosphamide for nonurological tumours, compared with 0.12% for those not treated with cyclophosphamide (representing a 9-fold increased risk) and 0.04% in the general population.[73] Another study of patients treated for non-Hodgkin's lymphoma found an incidence of 3.5% at 8 years, rising to 10.7% at 12 years.[74] The latency between ex-

posure to cyclophosphamide and development of TCC varies between 9 months and 23 years.[36,75] The risk of TCC appears to be dose-related, high-dose or protracted therapy carrying greater risk. No maximum 'safe' dose has been suggested. Pre-existing haemorrhagic cystitis may be a risk factor for bladder tumours,[38,70] but one large study showed no increased risk,[74] and the absence of haemorrhagic cystitis does not preclude the possibility of subsequent TCC. The risk of TCC means that careful consideration is necessary before using cyclophosphamide for treatment of benign conditions.[76]

Minimising the exposure of the urothelium to toxic metabolites of cyclophosphamide should decrease not only the incidence of haemorrhagic cystitis, but also TCC.[75] Methods of achieving this are discussed in section 3.1. Regardless of these measures, any patient previously treated with cyclophosphamide should undergo regular screening for TCC.[36]

4.2 Other Drugs

The combination of methotrexate and corticosteroids has been associated with TCC of the bladder in 2 cases.[77] Analgesic abuse is a recognised risk factor for TCC of the renal pelvis,[78] but no association is yet established with TCC of the bladder. Chlornaphazine for treatment of Hodgkin's disease has been associated with TCC in 2 cases.[79] Chlornaphazine is a derivative of 2-naphthylamine, a substance associated with occupationally-acquired TCC in the rubber and chemical industries. The drug has now been withdrawn.

5. Local Complications of Intravesical Treatment for Bladder Tumour

Intravesical agents are indicated for the treatment of carcinoma of the bladder where there is frequent recurrence, carcinoma *in situ* or residual disease. They are effective in reducing risk of tumour recurrence and have lower rates of systemic adverse effects than systemically administered drugs,[80] although systemic absorption can occur.

5.1 Antineoplastic Therapy

Agents are typically instilled for a 1 hour period weekly for 6 to 8 weeks. Some manufacturers warn that risk of adverse effects may be increased if instilled for excessive periods.

5.1.1 Mitomycin

Mitomycin is a cytotoxic antibiotic. Local adverse effects usually consist of frequency and dysuria.[81] Reduced bladder capacity has been reported in 22% of patients, which fails to reverse in one-third of patients and can be sufficiently severe to require cystectomy.[82] Dystrophic calcification of the bladder wall has been described,[83] but it has been disputed as to whether mitomycin is the cause of this.[84]

5.1.2 Doxorubicin

Chemical cystitis is frequent and may be severe enough to cause discontinuation of treatment in 20%,[85] especially in patients who have previously had radiotherapy. Macroscopic haematuria is seen in 20% of patients when doxorubicin is given in combination with mitomycin.[86] Macroscopic haematuria is rare when mitomycin is given alone. Bladder contracture has been described, with a recommendation for objective monitoring of bladder capacity during treatment.[87]

5.2 Immunotherapy

Bacillus Calmette-Guerin (BCG) is effective in the treatment of superficial bladder cancer. The precise mechanism of activity is not known but suggestions include immune stimulation by local inflammation or specific and nonspecific antitumour activity. Adverse effects are common during the weekly instillation period, but the majority are not serious and resolve shortly after the end of treatment.[88] About 5% of patients experience more serious adverse effects.[89] Local problems include frequency and dysuria in 59.5 to 88%, haematuria in 26 to 58%,[90,91] orchitis,[92] bladder contracture,[93] dystrophic calcification[90] and granulomatous prostatitis.[89] Problems are more common where there is bleeding, so instillation should be delayed after traumatic catheterisation

Table III. Drugs with suggested association with retroperitoneal fibrosis

Analgesics	Antihypertensives	Miscellaneous
Aspirin (acetylsalicyclic acid)	Hydralazine	Amphetamines
	Methyldopa	Haloperidol
Phenacetine	Reserpine	Anticonvulsants
Paracetamol (acetaminophen)	Hydrochlorothiazide	Antihistamines
		Ampicillin
Codeine		Glibenclamide (glyburide)

or trans-urethral resection of bladder tumour. The incidence of complications depends on the BCG strain employed, with the Connaught strain leading to the lowest percentage of patients requiring hospitalisation.[94] The use of isoniazid, aspirin (acetylsalicylic acid), antihistamines and antispasmodics for 1 day prior and 2 days post administration has been advocated to reduce incidence of adverse effects[92] but, potentially, this could reduce effectiveness of therapy. Occasionally it is necessary to give antituberculous agents for BCG cystitis.

6. Retroperitoneal Fibrosis

Retroperitoneal fibrosis (RPF) results in a midline plaque, typically at the aortic bifurcation. The fibrotic process often affects the ureters, but any nearby structure is at risk. The aetiology of the condition is unclear. 70% of cases are idiopathic, but suggested risk factors include peritonitis, malignancy, previous radiation therapy, auto-immune disease and drugs.[95] It is important to exclude these associations when the diagnosis is made. Treatment involves the use of corticosteroids and/or open surgery.

6.1 Ergot Alkaloids

An association between methysergide and RPF was first reported in 1964[96] and the link is now well established. High doses of bromocriptine and ergotamine may also cause RPF.

6.2 β-Blockers

Case reports have been published of RPF occurring in association with the following agents: atenolol,[97,98] metoprolol,[99] oxprenolol,[100] propranolol,[101] sotalol[102] and timolol.[103] However, there is no definite proof of an association.

6.3 Other Drugs

Other drugs that have been associated with RPF are listed in table III.

7. Ureteric Calculi

Any drug causing nephrolithiasis may cause ureteric calculi and drugs are estimated to cause 0.8 to 2.5% of all ureteric calculi.[104,105] Possible causative agents are listed in table IV. Agents which elevate urinary calcium or uric acid may cause stones. Antineoplastic agents may cause urate stones through lysis of tumour cells. Allopurinol is used to treat urate stones but may itself cause xanthine stones.[110] Triamterene and indinavir[111] can form stones of which the drug is the prime constituent.[106] Analgesics may cause stones through papillary necrosis.

8. Discolouration of Urine

Many foods and drugs can colour the urine (see table IV). Discolouration may lead to misdiagnosis

Table IV. Drugs potentially causing nephrolithiasis and ureteric calculi

Acetazolamide[110]
Allopurinol
Analgesics
Antineoplastic therapy
Colecalciferol (vitamin D)[110]
Corticosteriods[110]
Indinavir[111]
Nitrofurantoin[112]
Piridoxilate[109]
Probenecid[110]
Salicylates
Silicate antacids[105]
Sulfonamides[104]
Triamterene[104-108]

Table V. Drugs known to cause discolouration of the urine

Yellow-brown
Nitrofurantoin
Reddish
Benserazide-levodopa (co-beneldopa)
Carbidopa-levodopa (co-careldopa)
Levodopa
Danthron-docusate sodium (co-danthrusate)
Danthron-poloxamer 188 (co-danthramer)
Clofazimine
Orange-yellow
Sulfasalazine
Pink
Nefopam
Phenindione
Orange-red
Rifampicin (rifampin)
Rifabutin
Blue
Triamterene

of haematuria, resulting in unnecessary invasive investigation.

9. Conclusions

Many urological symptoms and conditions can be caused by drug treatment. Since many patients with urological conditions are elderly and may be taking several drugs, a pharmacological cause for their urinary symptoms should be considered. Where appropriate, a drug or its dose should be adjusted to see if symptoms resolve. Such an approach will avoid unnecessary and potentially morbid investigation in patients who may tolerate the procedure poorly.

References

1. Kiruluta HG, Andrews K. Urinary incontinence secondary to drugs. Urology 1983; 22: 88-90
2. Van Putten T, Malkin MD, Weiss MS. Phenothiazine-induced stress incontinence. J Urol 1973; 109: 625-6
3. Fuller MA, Borovicka MC, Jaskiw GE, et al. Clozapine-induced urinary incontinence: incidence and treatment with ephedrine. J Clin Psychiatry 1996; 57: 514-8
4. Marshall HJ, Beevers DG. Alpha-adrenergic blockade and urinary incontinence. J Hypertens 1993; 11: 1152-3
5. Marshall HJ, Beevers DG. α-Adrenoceptor blocking drugs and female urinary incontinence: prevalence and reversibility. Br J Clin Pharmacol 1996; 42: 507-9
6. Donker PJ, Ivanovici F, Noach EL. Analyses of the urethral pressure profile by means of electromyography and the administration of drugs. Br J Urol 1972; 44: 180-93
7. Thien TH, Delaere KPJ, Debruyne FMJ, et al. Urinary incontinence caused by prazosin. BMJ 1978; 1: 622-3
8. Fantl JA, Wyman JF, Wilson M, et al. Diuretics and urinary incontinence in community-dwelling women. Neurourol Urodyn 1990; 9: 25-34
9. Fossaluzza V, Di Benedetto P, Zampa A, et al. Misoprostol-induced urinary incontinence. J Intern Med 1991; 230: 463-4
10. Casanova JE. Incontinence after use of enalapril [letter]. J Urol 1990; 143: 1237-8
11. Jonville AP, Echenberger J, Dutertre JP, et al. Urapidil and enuresis [letter]. Lancet 1992; 339: 688
12. Bogle RG. Urapidil and the bladder [letter]. Lancet 1992; 339: 993
13. Milsom I, Ekelund P, Molander U, et al. The influence of age, parity, oral contraception, hysterectomy and menopause on the prevalence of urinary incontinence in women. J Urol 1993; 149: 1459-62
14. Evans JWH, Christmas TJ. Detrusor instability following colchicine therapy. Br J Urol 1991; 67: 552-3
15. Nakano M, Ishihara S, Deguchi T, et al. Fluoroquinolone associated bladder stone. J Urol 1997; 157: 946
16. Pras E, Stienlauf S, Pinkhas J, et al. Urinary retention associated with Ipratropium Bromide. Ann Pharmacother 1991; 25: 939-40
17. Stallard S, Prescott S. Postoperative urinary retention in general surgical patients. Br J Surg 1988; 75: 1141-3
18. Petersen TK, Husted SE, Rybro L. Urinary retention during i.m. and extradural morphine analgesia. Br J Anaesth 1982; 54: 1175-8
19. Hodsman NBA, Kenny GNC, McArdle CS. Patient controlled analgesia and urinary retention. Br J Surg 1988; 75: 212
20. Niemi L, Pitkanen M, Tuominen M, et al. Technical problems and side effects associated with continuous intrathecal or epidural post-operative analgesia in patients undergoing hip arthroplasty. Eur J Anaesth 1994; 11: 469-74
21. Lejus C, Roussiere G, Testa S, et al. Postoperative extradural analgesia in children: comparison of morphine with fentanyl. Br J Anaesth 1994; 72: 156-9
22. Rawal N, Mollefors K, Axelsson K, et al. An experimental study of the urodynamic effects of epidural morphine and of naloxone reversal. Anesth Analg 1983; 62: 641-7
23. Petros JG, Bradley TM. Factors influencing postoperative urinary retention in patients undergoing surgery for benign anorectal disease. Am J Surg 1990; 159: 374-6
24. Baumgarten RK. Spinal anaesthesia and postoperative urinary retention in patients with benign anorectal disease [letter]. Am J Surg 1994; 167: 457
25. Rawal N, Mollefors K, Axelsson K, et al. Naloxone reversal of urinary retention after epidural morphine. Lancet 1981; II: 1411
26. Bowers FJ, Hartmann R, Khanduja, et al. Urecholine prophylaxis for urinary retention in anorectal surgery. Dis Colon Rectum 1986; 30: 41-2
27. Lin AYF, Zantz G, Myssiorek D. Astemizole associated urinary retention. Otolaryngol Head Neck Surg 1991; 104: 893-4
28. Punja MK, Sklarew PR, Sutherland R, et al. The effect of terfenadine on urination [abstract]. J Allergy Clin Immunol 1992; 91: 346
29. Kumar SA, Spaulding HS, Sutherland RS, et al. The effect of chlorpheniramine maleate on urinary retention in men with

symptomatic benign prostatic hypertrophy [abstract]. J Allergy Clin Immunol 1994; 93: 177
30. Friedman AJ. Acute urinary retention after gonadotrophin-releasing hormone agonist treatment for leiomyomata uteri. Fertil Steril 1993; 59: 677-8
31. Kohli-Kumar M, Pearson ADJ, Sharkey I, et al. Urinary retention-an unusual dystonic reaction to continuous metoclopramide infusion. Ann Pharmacother 1991; 25: 469-70
32. Committee on Safety of Medicines. Nefopam hydrochloride (Acupan). Curr Probl 1989 Jan; 24
33. Nussinovitch M, Soen G, Volovitz I, et al. Urinary retention related to phenytoin therapy. Clin Pediatr 1995; 34: 382-3
34. Cohen MAA, Alfonso CA, Mosquera M. Development of urinary retention during treatment with clozapine and meclizine [letter]. Am J Psychiatry 1994; 151: 619-20
35. Coggins PR, Ravdin RG, Eisman SH. Clinical pharmacology and preliminary evaluation of cytoxan (cyclophosphamide). Cancer Chemother Rep 1959; 3: 9-11
36. Levine LA, Richie JP. Urological complications of cyclophosphamide [letter]. J Urol 1989; 141: 1063-9
37. Watson NA, Notley RG. Urological complications of cyclophosphamide. Br J Urol 1973; 45: 606-9
38. Stillwell TJ, Benson RC. Cyclophosphamide-induced hemorrhagic cystitis: a review of 100 patients. Cancer 1988; 61: 451-7
39. Bennett AH. Cyclophosphamide and hemorrhagic cystitis. J Urol 1974; 11: 603-6
40. Reynolds RD, Simerville JJ, O'Hara DD, et al. Hemorrhagic cystitis due to cyclophosphamide. J Urol 1969; 101: 45-7
41. Cox PJ. Cyclophosphamide cystitis: identification of acrolein as the causative agent. Biochem Pharmacol 1979; 28: 2045-9
42. Drollier MJ, Saral R, Santos G. Prevention of cyclophosphamide-induced hemorrhagic cystitis. Urology 1982; 20: 256-8
43. Frasier LH, Kanekal S, Keher JP. Cyclophosphamide toxicity. Drugs 1991; 42: 781-95
44. Hows JM, Mehta A, Ward L et al. Comparison of mesna with forced diuresis to prevent cyclophosphamide induced hemorrhagic cystitis in marrow transplantation: a prospective randomised study. Br J Cancer 1984; 50: 753-6
45. Sladek NE, Smith PC, Bratt PM, et al. Influence of diuretics on urinary general base catalytic activity and cyclophosphamide-induced bladder toxicity. Cancer Treat Rep 1982; 66: 1889-900
46. Miller LJ, Chandler SW, Ippoliti CM. Treatment of cyclophosphamide-induced hemorrhagic cystitis with prostaglandins. Ann Pharmacother 1994; 28: 590-4
47. Levine LA, Kranc DM. Evaluation of carboprost tromethamine in the treatment of cyclophosphamide-induced hemorrhagic cystitis. Cancer 1990; 66: 242-5
48. Jerkins GR, Noe HN, Hill D. Treatment of complications of cyclophosphamide cystitis. J Urol 1988; 139: 923-5
49. Shurafa M, Shumaker E, Cronin S. Prostaglandin $F_{2\alpha}$ bladder irrigation for control of intractable cyclophosphamide-induced hemorrhagic cystitis. J Urol 1987; 137: 1230-1
50. Liu YK, Harty JI, Steinbock GS, et al. Treatment of radiation or cyclophosphamide induced hemorrhagic cystitis using conjugated estrogen. J Urol 1990; 144: 41-3
51. Shameem IA, Shimabukuro T, Shirataki S, et al. Hyperbaric oxygen therapy for control of intractable cyclophosphamide-induced hemorrhagic cystitis. Eur Urol 1992; 22: 263-4
52. Ahmed M, Davison OW. Severe cystitis associated with tiaprofenic acid. BMJ 1991; 303: 1376
53. Crawford MLA, Waller PC, Wood SM. Severe cystitis associated with tiaprofenic acid. Br J Urol 1997; 79: 578-84
54. Greene GF, Millard OH, Norman RW, et al. Cystitis associated with tiaprofenic acid. J Urol 1994 Oct; 152: 1101-2
55. O'Neill GFA. Tiaprofenic acid as a cause of non-bacterial cystitis. Med J Aust 1994; 160: 123-5
56. Henley MJ, Harriss D, Bishop MC. Cystitis associated with tiaprofenic acid: a survey of British and Irish urologists. Br J Urol 1997; 79: 585-7
57. Australian Adverse Drug Reactions Advisory Committee. Update on tiaprofenic acid and urinary symptoms. Australian Adverse Drug Reaction Bulletin 1994; 13: 6
58. Crew JP, Donat R, Roskell D, et al. Bilateral ureteric obstruction secondary to prolonged use of tiaprofenic acid. Br J Clin Pract 1997; 51 (1): 59-60
59. Bateman DN. Tiaprofenic acid and cystitis. BMJ 1994; 309: 552-3
60. Ghose K. Cystitis and non-steroidal anti inflammatory drugs: an incidental association or an adverse effect. N Z Med J 1993; 106: 501-3
61. Andriole GL, Brickman C, Lack EE, et al. Danazol-induced cystitis; an undescribed source of hematuria in patients with hereditary angioneurotic edema. J Urol 1986; 135: 44-6
62. Nakada TN, Ishikawa S, Sakamota M. N-(3′,4′-dimethoxycinnamoyl) anthranillic acid, an antiallergic compound, induced eosinophilic cystitis. Urol Int 1986; 41: 457-64
63. Bramble FJ, Morley R. Drug-induced cystitis: the need for vigilance. Br J Urol 1997 Jan; 79: 3-7
64. Moller NE. Carbenicillin-induced haemorrhagic cystitis [letter]. Lancet 1978; II: 946
65. Forni A, Koss LG, Geller W. Cytological study of the effect of cyclophosphamide on the epithelium of the urinary bladder in man. Cancer 1964; 17: 1348-55
66. Worth PHL. Cyclophosphamide and the bladder [letter]. BMJ 1971; 3: 182
67. Dale GA, Smith RB. Transitional cell carcinoma of the bladder associated with cyclophosphamide. J Urol 1974; 112: 603-4
68. Ansell ID, Castro JE. Carcinoma of the bladder complicating cyclophosphamide therapy. Br J Urol 1975; 47: 413-8
69. Richtsmeier AJ. Urinary bladder tumors after cyclophosphamide. N Engl J Med 1975; 293: 1045-6
70. Seo IS, Clark SA, McGovern FD. Leiomyosarcoma of the urinary bladder 13 years after cyclophosphamide therapy for Hodgkin's disease. Cancer 1985; 55: 1597-603
71. Chasko SB, Keuhnelian JG, Gutowski WT. Spindle cell cancer of bladder during cyclophosphamide therapy for Wegener's granulomatosis. Am J Surg Pathol 1980; 4: 191-6
72. Wall RL, Clausen KP. Carcinoma of the urinary bladder in patients receiving cyclophosphamide. N Engl J Med 1975; 293: 271-3
73. Fairchild WV, Spence CR, Soloman HD, et al. The incidence of bladder cancer after cyclophosphamide therapy. J Urol 1979; 122: 163-4
74. Pedersen-Bjergaard J, Ersboll J, Hansen VL, et al. Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. N Engl J Med 1988; 318: 1028-32
75. Cannon J, Linke CA, Cos LR. Cyclophosphamide-associated carcinoma of urothelium: modalities for prevention. Urology 1991; 38: 413-6
76. Elliott RW, Essenhigh DM, Morley AR. Cyclophosphamide treatment of systemic lupus erythematosus: risk of bladder cancer exceeds benefit. BMJ 1982; 284: 1160-1
77. Millard RJ, McCredie S. Bladder cancer in patients on low-dose methotrexate and corticosteroids [letter]. Lancet 1994; 343: 1222-3

78. Bengtsson U, Angervall L, Ekman H, et al. Transitional cell tumors of the renal pelvis in analgesic abusers. Scand J Urol Nephrol 1968; 2: 145-50
79. Laursen B. Cancer of the bladder in patients treated with chlornaphazine. BMJ 1970; 3: 684-5
80. Soloway MS. Introduction and overview of intravesical therapy for superficial bladder cancer. Urology 1988; 31 Suppl. 3: 5-16
81. Nissenkorn I, Herrod H, Soloway MS. Side effects associated with intravesical Mitomycin C. J Urol 1981; 126: 596-7
82. Eijsten A, Knonagel H, Hotz E, et al. Reduced bladder capacity in patients receiving intravesical chemoprophylaxis with mitomycin C. Br J Urol 1990; 66: 386-8
83. Drago PC, Badalament RA, Lucas J, et al. Bladder wall calcification after intravesical mitomycin C treatment of superficial bladder cancer. J Urol 1989; 142: 1071-2
84. Dore B, Aubert J. Re: bladder wall calcification after intravesical mitomycin C treatment of superficial bladder cancer [letter]. J Urol 1991; 145: 1277
85. Lundbeck F, Morgensen P, Jeppesen N. Intravesical therapy of non-invasive bladder tumours (stage Ta) with doxorubicin and urokinase. J Urol 1983; 130: 1087-9
86. Fukui I, Sekine H, Kihara K. Intravesical combination chemotherapy with Mitomycin C and doxorubicin for carcinoma in situ of the bladder. J Urol 1989; 141: 531-4
87. Dmochowski R, Rudy DC. Bladder contracture following intravesical doxorubicin therapy: case report and review of the literature. J Urol 1990; 143: 816-8
88. Lamm DL, van der Meijden APM, Morales A, et al. Incidence and treatment of complications of Bacillus Calmette-Guerin intravesical therapy in superficial bladder cancer. J Urol 1992; 147: 596-600
89. Moss JT, Kadmon D. BCG and the treatment of superficial bladder cancers. DICP Ann Pharmacother 1991; 25: 1355-67
90. Spirnak JP, Lubke WL, Thompson IM, et al. Dystrophic bladder wall calcifications following intravesical BCG treatment for superficial transitional cell carcinoma of the bladder. Urology 1993; 42: 89-92
91. Herr HW, Pinsky CM, Whitmore WF, et al. Experience with intravesical bacillus Calmette-Guerin therapy of superficial bladder tumors. Urology 1985; 25: 119-23
92. Pansadoro V, de Paula F. Intravesical Bacillus Calmette-Guerin in the treatment of superficial transitional cell carcinoma of the bladder. J Urol 1987; 138: 299-301
93. Grossman HB. Bladder contracture following intravesical BCG immunotherapy. Urology 1993; 41 353-5
94. Lamm DL, Stogdill VD, Stogdill BJ, et al. Complications of Bacillus Calmette-Guerin immunotherapy in 1,278 patients with bladder cancer. J Urol 1986; 135: 272-4
95. van Bommel EFH, Boeve ER, Weimar W. European Board of Urology. Retroperitoneal fibrosis: current concepts. Eur Urol (Update Series) 1993; 2: 18-23
96. Graham JR. Methysergide for prevention of headaches: experience of 500 patients aver 3 years. N Engl J Med 1964; 270; 67-72
97. Doherty CC, McGeown MG, Donaldson RA. Retroperitoneal fibrosis after treatment with atenolol [letter]. BMJ 1978; 2: 1786
98. Johnson JN, McFarland J. Retroperitoneal fibrosis associated with atenolol [letter]. BMJ 1980; 280: 864
99. Thompson J, Julian DG. Retroperitoneal fibrosis associated with metoprolol. BMJ 1982; 284: 83-4
100. McCluskey DR, Donaldson RA, McGeown MG. Oxprenolol and retroperitoneal fibrosis [letter]. BMJ 1980; 281: 1459-60
101. Pierce JR, Trostle DC, Warner JJ. Propranolol and retroperitoneal fibrosis [letter]. Ann Intern Med 1981; 95: 244
102. Laakso M, Arvala I, Tervonen S. Retroperitoneal fibrosis associated with sotalol [letter]. BMJ 1982; 285: 1085-6
103. Rimmer E, Richens A, Forster ME. Retroperitoneal fibrosis associated with timolol [letter]. Lancet 1983; I: 300
104. Daudon M, Reveillaud RJ. Drug nephrolithiasis: an unrecognised and underestimated pathology. In: Schwille PO, Smith LH, Robertson WG, et al., editors. Urolithiasis and related clinical research. New York: Plenum Press, 1985: 371-4
105. Rapado A, Traba ML, Caycho C, et al. Drug-induced renal stones: incidence, clinical expression and stone analysis. Contrib Nephrol 1987; 58: 25-9
106. Sorgel F, Ettinger B, Benet LZ. The true composition of kidney stones passed during triamterene therapy. J Urol 1985; 134: 871-3
107. Grunberg RW, Silberg SJ. Triamterene-induced nephrolithiasis [letter]. JAMA 1981; 245: 2494-5
108. Ettinger B, Oldroyd NO, Sorgel F. Triamterene nephrolithiasis. JAMA 1980; 244: 2443-5
109. Daudon M, Reveillaud R-J, Normand M, et al. Piridoxilate-induced calcium oxalate calculi: a drug-induced metabolic nephrolithiasis. J Urol 1987; 138: 258-61
110. Curtis JR. Drug-induced renal disease. Drugs 1979; 18: 377-91
111. Kopp JB, Miller KD, Mican JA, et al. Crystalluria and urinary tract abnormalities associated with indinavir. Ann Intern Med 1997; 127: 119-25
112. MacDonald JB, MacDonald ET. Nitrofurantoin crystalluria. BMJ 1976; 2: 1044-5

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