Adverse drug reactions and urological disease

KARAMJIT BADYAL, CHRISTOPHER ANTON AND ROBIN FERNER

Despite the significant benefits of today’s drugs, they still have the potential to cause significant adverse effects. Here the authors briefly review urological disorders caused by drugs and adverse reactions caused by drugs used to treat urological disorders.

An adverse drug reaction is a response to a drug that is harmful and unintended. The World Health Organization defines this as ‘a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.’

Drugs and their metabolites are excreted in the urine. As urine is stored in the bladder, sometimes for prolonged periods, this can lead to unwanted effects. Micturition and sexual function are complex, and influenced by several pharmacological receptors, so that many drugs can interfere with these processes.

UROLOGICAL PROBLEMS CAUSED BY DRUGS

Adverse drug reactions may present as urological disorders. Since the disorder can occur after prolonged exposure, or be unrelated to the therapeutic pharmacology of the drug, the causal role of the drug may be hidden. This emphasises the value of a thorough drug history to ascertain whether the presenting symptoms could be due to a drug.

Renal crystals and calculi

Drugs can cause kidney stones, and perhaps 2% of all cases result from drug treatment (Figure 1). Drugs that are renally excreted can crystallise in the urine if they are poorly soluble. Sulfonamides can precipitate in acid urine, as can methotrexate and the potassium-sparing diuretic triamterene. Indinavir (Crixivan), used to treat HIV infection, by contrast crystallises in alkaline urine. Other drugs have been identified by analysing the renal stone for evidence of the drug or its metabolites. Daudon et al listed 24 different drugs, including amoxicillin, quinolones, antacids and allopurinol.

Figure 1. Certain drugs can cause renal calculi, so it is important to take a detailed medication history (photo courtesy of Jayne Douglas-Moore)
Urinary calculi can also occur due to the metabolic effects of drugs. Calcium salts, especially when combined with vitamin D supplements, can increase urinary calcium concentration and contribute to stone formation. Acetazolamide, a drug used to treat glaucoma, blocks the reabsorption of bicarbonate in the proximal renal tubule, which can result in alkaline urine and a hyperchloremic metabolic acidosis. The alkaline urine promotes precipitation of calcium phosphate.

Calculi have been reported in patients with cystic fibrosis on long-term antibiotics. This can be because antibiotics alter the gut flora, so micro-organisms that degrade oxalate ions may no longer be present. An excess of these ions causes poorly soluble calcium oxalate to precipitate.

Other drugs that have been associated with metabolically induced renal calculi include furosemide, pyridoxine, antacids and corticosteroids.\(^7\)

**Urinary tract infection**

Bacterial infections are a major cause of morbidity and mortality in post-transplant patients due to the immunosuppressed state induced by drugs. Reports of this have been linked with corticosteroid use, azathioprine and ciclosporin.\(^4\) Urinary tract infections, followed by bacteraemia and epididymo-orchitis, were reported in a case of a 56-year-old patient with systemic lupus erythematosus on azathioprine and prednisolone.\(^4\)

Sodium-glucose cotransporter 2 (SGLT2) inhibitors include the drugs canagliflozin (Invokana), dapagliflozin (Forxiga) and empagliflozin (Jardiance). These antidiabetic drugs promote urinary glucose excretion by inhibiting glucose reabsorption in the kidney. Raised glucose concentrations in the urine have been shown to increase the risk of urinary tract infections in a safety study based on the results of 12 randomised, placebo-controlled trials. However, most cases were mild to moderate and responded to a single course of antibiotic treatment.\(^5,6\)

**Erectile dysfunction**

Many drugs can cause or exacerbate erectile dysfunction (ED), most commonly psychotropic and antihypertensive drugs. Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and venlafaxine, and antipsychotics such as risperidone and olanzapine, have been implicated as causative agents. The pharmacological mechanisms are unclear.\(^7\) The diagnosis of drug-induced ED is difficult in this setting, as depression also causes erectile dysfunction.\(^8\)

ED mainly affects men over 40. This age group is also more likely to be on antihypertensive drugs such as ACE inhibitors, calcium-channel blockers, beta-blockers and thiazide diuretics, all of which have been associated with ED; however, it is unclear whether the association is causal. Statins, which are commonly co-prescribed in patients at elevated cardiovascular risk, have also been implicated.\(^7\)

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic drugs</td>
<td>Chlorpromazine, risperidone, clozapine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Tricyclic antidepressants: amitriptyline, dosulepin</td>
</tr>
<tr>
<td></td>
<td>SSRI – fluoxetine, fluvoxamine, citalopram</td>
</tr>
<tr>
<td></td>
<td>SNRI – reboxetine</td>
</tr>
<tr>
<td>Antiparkinsonian agents</td>
<td>Amantadine, monoamine oxidase B inhibitors, catechol-O-methyltransferase inhibitors, levodopa, dopamine agonists</td>
</tr>
<tr>
<td>Antiarhythmic drugs</td>
<td>Disopyramide and flecainide</td>
</tr>
<tr>
<td>Antispasmodics</td>
<td>Hyoscine butylbromide</td>
</tr>
<tr>
<td>Antimuscarinic bronchodilators</td>
<td>Ipratropium, tiotropium, glycopyrronium inhaler</td>
</tr>
<tr>
<td>Anticholinergic drugs used</td>
<td>Oxybutynin, fesoterodine, flavoxate, solifenacin, trolsium, tolterodine</td>
</tr>
<tr>
<td>to treat overactive bladder</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.** Drugs with anticholinergic activity that depress detrusor activity and can cause urinary retention and overflow incontinence

**Urinary retention**

Many drugs can interfere with the complex process of micturition, resulting in urinary retention or urinary incontinence. Drugs that have anticholinergic activity block the parasympathetic pathway and can then impair the contraction of the detrusor muscle. Relevant drugs that have been associated with urinary retention are listed in Table 1.

Urinary retention can be caused by drugs that do not have an anticholinergic effect – the antiarrhythmic drug flecainide, for example. While an anticholinergic effect is possible, this drug is excreted largely unmetabolised in the urine, and a local anaesthetic effect on the bladder mucosa has been suggested.

Muscle relaxant effects of benzodiazepines may impair micturition, as has been reported in patients taking clonazepam and diazepam.\(^9\) The effects of opioids, which are most likely to cause problems in patients post-operatively, are partly caused by relaxation of bladder wall muscle; they may also mask the sensation of bladder fullness, and
increase the resistance in the bladder outflow tract.9

Pseudoephedrine, a drug found in many over-the-counter cold remedies, is an adrenergic agonist. It binds to receptors in the proximal urethra, increasing internal sphincter tone and so exacerbating voiding difficulties. Cold remedies containing pseudoephedrine may be taken with anticholinergic antihistamines, further increasing the risk of urinary retention.9

Calcium-channel blockers reduce smooth muscle contractility in the bladder by inhibiting calcium influx. There are several case reports of urinary retention associated with calcium-channel blockers. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis in the bladder, which may also result in urinary retention.9

Urinary incontinence
Many drugs cause urinary incontinence. Drugs that depress detrusor activity (Table 1), causing retention and overflow obstruction, can present with incontinence. So too can drugs such as diuretics, caffeine and alcohol that increase detrusor activity and cause motor urge incontinence (Table 2). Stress incontinence in females can be caused by alpha-blockers such as doxazosin.10

Elderly patients are more susceptible to the adverse effects of drugs and are more likely to be taking multiple medicines. It may be possible to alleviate symptoms by reducing drug doses or finding suitable alternative treatment.10

Retroperitoneal fibrosis
Methysergide is an ergot derivative whose use is restricted to the prevention of severe intractable headaches. It causes the rare condition of retroperitoneal fibrosis, in which there is extensive fibrosis of tissues in the retroperitoneum.11,12 This can lead to ureteric obstruction.13 The variable presentation of retroperitoneal fibrosis as backache, abdominal pain, hydrocoele, oedema or anuria can delay diagnosis.12 Other ergot derivatives used in the treatment of Parkinson’s disease, including pergolide, bromocriptine and cabergoline, are rare causes of retroperitoneal fibrosis.

Haemorrhagic cystitis
High-dose cyclophosphamide therapy leads to the urinary excretion of sufficient acrolein, a toxic metabolite, to cause haemorrhagic cystitis in up to 20% of unprotected patients. Fortunately, mesna, (2-mercaptoethane sulphonate sodium), also renally excreted, reacts with acrolein to form a non-toxic compound.14 Mesna treatment has greatly reduced the incidence of cyclophosphamide-induced haemorrhagic cystitis.

Ketamine-induced cystitis
Ketamine is an N-methyl-d-aspartate (NMDA) antagonist used as a dissociative anaesthetic. Ketamine abuse causes severe damage to the urinary tract. The bladder shrinks, and there is histological evidence of chronic inflammation, sometimes with mucosal ulceration and sometimes with gross haematuria. The result of ketamine damage is very marked urinary frequency. The harm may be linked to the presence of NMDA receptors in the urinary tract.15

<table>
<thead>
<tr>
<th>Effects</th>
<th>Type of drugs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase urine production</td>
<td>Alcohol</td>
<td>Wine, beer, spirits</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>Coffee, tea, chocolate, some soft drinks</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>Furosemide, thiazides, bumetanide</td>
</tr>
<tr>
<td>Interfere with bladder</td>
<td>Cholinesterase inhibitors</td>
<td>Neostigmine</td>
</tr>
<tr>
<td>contractility and contribute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>to urge incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interfere with bladder</td>
<td>Opioids</td>
<td>Morphine, codeine, oxycodone</td>
</tr>
<tr>
<td>contraction and can cause</td>
<td>Anticholinergics</td>
<td>Antihistamines, tricyclic antidepressants, procyclidine, benzatropine,</td>
</tr>
<tr>
<td>urinary retention and</td>
<td></td>
<td>orphenadrine</td>
</tr>
<tr>
<td>overflow incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tighten urinary sphincter</td>
<td>Alpha-blockers</td>
<td>Doxazosin</td>
</tr>
<tr>
<td>and can cause urinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>retention and stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>incontinence in women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce awareness of the</td>
<td>Sedatives and hypnotics</td>
<td>Zopiclone, benzodiazepines</td>
</tr>
<tr>
<td>need to urinate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Mechanisms of drug-induced incontinence and the drugs implicated

ADVERSE UROLOGICAL DRUG REACTIONS

Anticholinergics
Anticholinergic drugs used to treat detrusor instability have well documented adverse effects such as constipation, blurred mouth, dizziness, and also urinary retention as described above. Dry mouth appears to be the most commonly reported adverse effect. Modified-release preparations have been shown to lower the incidence.4

Anticholinergic drugs can precipitate acute angle closure glaucoma. Oxybutynin has been associated with nightmares – there have been four spontaneous reports of this reaction in children and one in an elderly woman.4 Hallucination and tachycardia have been reported in patients taking tolterodine.

Mirabegron
Mirabegron (Betmiga) is the first selective beta-3 adrenoceptor agonist to be marketed. Tachycardia and urinary tract infections have been common adverse events in clinical trials.16

www.trendsinmenshealth.com
5-alpha-reductase inhibitors

Finasteride and dutasteride are selective inhibitors of 5-alpha-reductase. They reduce prostatic concentrations of dihydrotestosterone and cause the prostate to shrink. Adverse drug reactions relating to sexual function are well documented and include change in libido, erectile dysfunction, and disorders of ejaculation and orgasm. Many patients have reported adverse reactions that persist for months or years after treatment discontinuation, a condition labelled 'post-finasteride syndrome'. Physical components of the syndrome include chronic fatigue, gynaecomastia, muscle atrophy, thinning skin, and penis and scrotal shrinkage. Cognitive and sexual symptoms also occur. The diverse symptoms, delayed onset and uncertain mechanism of this reaction make diagnosis and management difficult.

Mycobacterial infection from BCG

Intravesical BCG is used to reduce the risk of recurrence or progression of bladder tumours. Adverse effects include cystitis, haematuria, bladder contracture, granulomatous prostatitis and epididymo-orchitis. Systemic adverse effects are uncommon but can be severe. Military tuberculosis is a very rare complication of BCG instillation; anti-tuberculous chemotherapy is an effective treatment.

Antibiotics

Antibacterial colitis and antimicrobial resistance are well known adverse effects of long-term antibacterial prophylaxis. A rare adverse effect of nitrofurantoin is pulmonary fibrosis. Gentamicin, used to treat acute urinary tract infections, can cause ototoxicity and renal toxicity, especially if monitoring of gentamicin concentrations is inadequate, or if dosage calculations are based on actual body weight. This may seriously overestimate the dosage in obese patients, whose total body water is less than calculated.

TURP

Adverse events may also occur as a result of urological procedures. The irrigation involved in the transurethral resection of the prostate (TURP) procedure may lead to excessive absorption of the irrigation fluid, resulting in severe hyponatraemia. This has been reported to present as headaches, anxiety, confusion, dyspnoea, arrhythmia, hypotension and seizures, and can be fatal if not treated.

REPORTING ADVERSE DRUG REACTIONS

Understanding how medicines can cause harm in the real world helps to make future prescribing safer. If you suspect an adverse reaction to a drug your patient has taken, then you or the patient can report it to the Medicines and Healthcare Products Regulatory Agency (MHRA) through the Yellow Card Scheme. The Agency especially welcomes reports of suspected reactions to new drugs (marked by an inverted black triangle), drugs used in children, and to serious or previously unsuspected reactions. Paper cards are still available, but reports are more easily made via the website (https://yellowcard.mhra.gov.uk/) or using a smartphone app for Android or iPhone.

CONCLUSION

Adverse drug reactions can be difficult to predict and link to specific drugs and symptoms. Urological disorders can be caused by drugs, and a careful drug history and timeline of symptoms will help to make the diagnosis.

Declaration of interests: none declared.

REFERENCES


