DRUGS THAT MAY EXACERBATE AND THOSE USED TO TREAT LYMPHOEDEMA

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This article explores the potential for drugs which can cause oedema to exacerbate pre-existing lymphoedema. Guidance on the assessment and management of patients taking these drugs is given. Drugs which may be used to treat lymphoedema are also considered. Current evidence does not support the routine use of benzopyrones, selenium, or diuretics in the management of lymphoedema. There is, however, a place for the use of corticosteroids and diuretics in specific circumstances, such as in the oedema of advanced cancer.

Key words

Drugs
Benzopyrones
Diuretics
Selenium

Drugs which may cause peripheral oedema

Drugs which are known to cause oedema may exacerbate pre-existing chronic oedema such as lymphoedema. Examples include: worsening primary lymphoedema with the use of the combined oral contraceptive pill or a calcium channel blocker for co-existing hypertension; increased swelling in arm oedema secondary to breast cancer treatment when docetaxel chemotherapy is administered; and the exacerbation of immobility-related lymphovenous oedema in a patient with multiple sclerosis (MS) when given corticosteroids to treat the MS. Drugs which may be involved in these situations will be considered in the first part of this paper.

Is oedema a common unwanted effect of drugs?

A search of drug databases for drugs whose undesirable effects include oedema of all types (including pulmonary oedema and angioedema) revealed 930 examples quoted in the Summaries of Product Characteristics (SPCs) (Electronic Medicines Compendium, 2007), and 333 examples in the adverse reactions sections of Micromedex (2007). Some of these records relate to pulmonary and allergic-type oedemas, but these are not always clearly distinguished from peripheral oedema in the information given. It is not easy to determine how common or severe these effects are from the data provided, as there is no entirely consistent way in which these are reported. Indeed, for some drugs, the frequencies quoted in different sources are not the same, e.g:

- Amantadine: oedema in >10% of patients (Electronic Medicines Compendium, 2007) versus 'one report' of peripheral oedema and congestive cardiac failure reported in 0.1–1% (Micromedex, 2007)
- Anagrelide: oedema in 8.5–20.6% of patients (Micromedex, 2007) versus 0.1–1% (Electronic Medicines Compendium, 2007).

Generally in product literature, the frequency of side-effects may be described as in *Table 1* (British National Formulary [BNF], 2007) or in variations on this approach. In the BNF, clinically relevant side-effects tend to be listed in order of frequency, with the more common at the beginning. The severity of the problem may be reported in the individual SPCs. Information about the incidence of unwanted side-effects is less easily available for drugs which have been in use for many years than for those more recently introduced.

Which drugs are involved?

Drugs which may cause peripheral oedema are listed in *Table 2*.

It is clearly helpful to be aware of drugs which commonly cause oedema, but equally, commonly used drugs which rarely cause oedema may also be relevant in individual patients.

Table 1

Frequency of side-effects of drugs

Very common	>1 in 10 (>10%)
Common	1 in 100 to 1 in 10 (1–10%)
Uncommon	1 in 1000 to 1 in 100 (0.1–1%)
Rare	1 in 10,000 to 1 in 1000 (0.01–0.1%)
Very rare	<1 in 10,000 (<0.01%)

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Specific drug groups

A. Calcium channel blockers

These frequently cause ankle oedema in a dose-dependent manner by peripheral arteriolar vasodilation (*Table 2*). The effect may be transient.

B. Sex hormones and related compounds

These may cause oedema by fluid retention.

C. Corticosteroids

Corticosteroids, e.g. prednisolone, dexamethasone are well recognised to cause peripheral oedema by sodium and water retention (mineralocorticoid effect) (BNF, 2007). The degree of swelling depends upon the dose and duration of treatment.

Incidence of unwanted effects

The frequencies quoted in *Table 2* may require some interpretation, particularly if they are derived from placebo controlled trials. For example, the 14.4% given for raloxifene is taken from the Raloxifene Use for The Heart (RUTH) trial in older postmenopausal women, where peripheral oedema occurred in 14.4% (725/5044) of the raloxifene arm compared with 12.1% (610/5057) of the placebo arm ($p<0.001$) (Barrett-Connor et al, 2006). The 'placebo' figure here is remarkably high and is likely to reflect the patient group studied. The additional effect from the drug may therefore be relatively small. Similarly for orlistat, there was an incidence of 2.8% in the orlistat arm compared with 1.9% in the placebo arm of the trial described in the product information (Micromedex, 2007).

The situation is particularly complicated for some drugs. For example, for rosiglitazone, the frequency is reported as 4.8% overall when it is used as monotherapy for diabetes. However, in combination with insulin, the frequency is increased (14.7%), as it is also with sulfonylureas (12.4%) (Micromedex, 2007).

How do the drugs cause oedema?

Oedema occurs in tissues when capillary filtration exceeds lymphatic drainage (Stanton, 2000). In patients with normal functioning lymphatics,

Table 2

Drugs which may cause oedema and the frequency of this (%) where available

Drug category	Examples	Frequency (%)	Dose per day (where relevant)
Calcium antagonists	Amlodipine	10.8 3 1.8	10mg 5mg 2.5mg
	Felodipine	17.4 8.8 2	10mg 5mg 2.5mg
	Nifedipine	7–50	up to 180mg
	Diltiazem	4.9–7	up to 360mg
Corticosteroids	Prednisolone Dexamethasone Fludrocortisone		
Non-steroidal anti-inflammatories (NSAIDs)	Diclofenac Ibuprofen Naproxen Celecoxib	1–3 1–3 3–9 2–3	
Alpha blockers	Doxazosin	4	
Sex hormones and related compounds	Oestrogens: ▸▸ combined oral contraceptive pill ▸▸ hormone replacement therapy ▸▸ diethylstilboestrol	>1	
	Anastrozole	7–10	1mg
	Tamoxifen	8–9	20mg
	Megestrol	14	160mg
	Bicalutamide	13	
	Raloxifene	14.4	
	Tibolone	5.7	
	Medroxyprogesterone acetate		
	Letrozole		
	Testosterone		
	Nandrolone		
Other hormones and related compounds	Somatropin	13–50	
	Paricalcitol	7	
Anticonvulsants	Gabapentin	1.7	
	Pregabalin	5–12	
Antidepressants	Trazodone	10	
	Mirtazapine	2	
	Paroxetine	<0.01	
	Monoamine oxidase inhibitors (MAOIs), e.g. phenelzine	'common'	

Table 2 cont

Drugs which may cause oedema and the frequency of this (%) where available

Drug category	Examples	Frequency (%)	Dose per day (where relevant)
Antidiabetics	Rosiglitazone	4.8(*)	
	Pioglitazone	5	
Anti-parkinsonians	Amantadine	>10	
	Cabergoline	1	
	Ropinirole	7	
Antipsychotics	Fluphenazine	'reported'	
	Risperidone	16	
	Olanzapine	1–10	
	Lithium	'reported'	
Biphosphonates	Zoledronic acid	21	
	Risedronate	4–6	
	Tiludronate	2.7	
Cytotoxics chemotherapy agents	Docetaxel	47–64	
Proton pump inhibitors	Esomeprazole	>0.1, >1	
	Omeprazole	<0.1	
	Lansoprazole and pantoprazole	'reported'	
Others	Anagrelide	8.5–20.6	
	Atorvastatin	2	
	Baclofen	>1, <10	
	Cilostazol	7–9	
	Ciprofloxacin	>0.01, <0.1	
	Etretinate	1–10	
	Glatarimer acetate	>1, <10	
	Isosorbide dinitrate	'reported'	
	Itroconazole	4	
	Metoclopramide	'reported'	
	Nicotinic acid	>0.1, <1	
	Orlistat	2.8(*)	
	Pentoxifylline	<1	
	Sirolimus	>10	
	Tacrolimus	>1, <10	
	Voriconazole	>10	

Notes: (*) see section in text on incidence of unwanted effects; 'reported' means it has been described in a small number of patients; where this is conflicting information the highest figure is given

drugs can cause oedema by increasing capillary filtration enough to overwhelm the capacity of the lymphatic system to drain the extra fluid. In patients with lymphoedema, the increased capillary filtration will overload the failing lymphatics further, resulting in increased oedema.

Capillary filtration is commonly increased by drugs because they cause an increase in the hydrostatic pressure in the capillaries, e.g. by increasing fluid retention and blood volume (e.g. corticosteroids, other hormones, non-steroidal anti-inflammatory drugs [NSAIDs]), or by causing peripheral arteriolar vasodilation (e.g. alpha blockers, calcium channel blockers).

For some drugs, the unwanted effect is a by-product of the mechanism of action required to treat a particular condition, e.g. alpha blockers used for hypertension. For others, the side-effect may be unexpected as it is not predicted from the known mechanisms of action, e.g. anticonvulsants. For some, e.g. etretinate, the causal relationship is not clear.

The practical aspects of assessing a drug's involvement in individual cases

When assessing patients with lymphoedema and other chronic oedemas, it is important to consider the drugs which they may be taking for other conditions, and whether these may be affecting their swelling. The duration of taking the medication and the timing between starting it and the appearance or exacerbation of the oedema should be taken into account.

Drugs which are commonly recognised to cause oedema are considered here but the list is not exhaustive. For any patient it is worth considering drug effects, particularly if the patient reports a worsening of his/her swelling after commencing a new medication, even if the medication taken does not appear in *Table 2*. The Electronic Medicines Compendium (2007) or Micromedex (2007) can be checked for rarer side-effects.

In patients with arm oedema, the legs should be examined for oedema as this may arise from fluid retention due to medication. In those with unilateral leg lymphoedema, examination of the unaffected leg is recommended.

For many patients, the drugs concerned may be essential to treat coexisting conditions but, if the oedema is severe, it may be necessary

to consider whether the drug could be discontinued or changed to an alternative which is less likely to cause swelling. For some drugs, e.g. calcium antagonists (*Table 2*), a dose reduction may be helpful. When drug doses are reduced, it may take some time for the oedema to improve, e.g. following a reduction in the dose of an oral corticosteroid.

In some cases, where there is fluid retention and the drug cannot be withdrawn or the dose reduced, the addition of a diuretic, e.g. furosemide may help reduce some of the oedema (BNF, 2007). However, this would not be appropriate when fluid retention is not the mechanism by which the drug causes oedema, e.g. calcium antagonists or alpha blockers.

In many cases, however, it is possible that patients who take oedema-causing drugs may not notice any effect on their pre-existing chronic oedema and, therefore, no changes need to be made.

Finally, in some cases, a medication may be the sole cause of peripheral oedema and, if so, the withdrawal of the responsible drug should result in the resolution of the swelling.

Conclusions

Patients with lymphoedema who are taking medication which may cause oedema should be assessed to determine whether the medication is exacerbating the swelling. If so, consideration should be given to dose reduction or changing medication if possible.

Drugs for the treatment of lymphoedema

The current treatment for lymphoedema mainly consists of the use of a combination of physical therapies (compression, massage and exercises) (Lymphoedema Framework, 2006), but a number of drug treatments have been advocated. Drugs for the treatment of complications such as cellulitis and topical preparations for skin conditions, e.g. emollients, antifungals and topical steroids are beyond the scope of this article.

The following drugs for the treatment of lymphoedema will be considered:

- Benzopyrones
- Selenium
- Diuretics
- Corticosteroids
- Pentoxifylline and vitamin E
- Hyperbaric oxygen.

The term lymphoedema covers a variety of aetiologies (e.g. primary and secondary lymphoedemas) and if the broader term chronic oedema is used, the range is even greater, e.g. includes lymphovenous oedemas (Moffatt et al, 2003). In addition, many patients, particularly the elderly, have co-morbidities, e.g. immobility which may exacerbate their swelling. It therefore seems unlikely that a single drug is going to reduce the swelling in all patients. In addition, the wide range of aetiologies makes it difficult to carry out large enough studies to demonstrate benefits for the different patient groups. Many of the studies to date have focused on patients with arm oedema secondary to the treatment of breast cancer (see below), as this is a relatively well-defined group. However, it may not be possible to extrapolate results from this group to others, such as those with primary lymphoedema, where the pathology may be very different.

Benzopyrones

The benzopyrones are a large group of thousands of substances, many of which naturally occur in plants (Twycross, 2000). There are two main groups:

- Coumarin and its derivatives (coumerols or alpha-pyrones)
- Flavone and its derivatives (flavonoids or gamma-pyrones).

A number of benzopyrones (naturally occurring, synthetic and semi-synthetic) have been developed for use in venous disease. However, there has also been interest in a possible role for them in the management of lymphoedema.

Examples of these drugs are given in *Table 3*. This list represents only a small percentage of all the different benzopyrones but includes those which have been investigated for use in lymphoedema.

Benzopyrones can be given orally and have also been used topically (Casley-Smith, 1999). They have been advocated by a number of authors, particularly Casley-Smith, 1999 and Twycross, 2000, but have not found their way into routine clinical practice in the UK. Casley-Smith (1999) described them as slow, but effective, cheap and convenient. He felt compression garments were unnecessary with them and that side-effects were minimal except for idiosyncratic hepatitis with coumarin (0.3%). However, a Cochrane review of published trials concluded that the current evidence did not support their routine use in lymphoedema (Badger et al, 2003).

Possible mechanism of action in lymphoedema

The actions of coumerols relevant to lymphoedema are (Twycross, 2000):

- Reduced blood vascular permeability to proteins by adherence of the drugs or metabolites to the endothelium of small blood vessels
- Stimulation of the local accumulation of macrophages in

Table 3

Examples of different benzopyrones

A. Coumerols:
- coumarin

B. Flavonoids:
- flavone
- diosmin
- flavan and its derivatives, e.g. hesperidin
- quercetin and its derivative rutin, and its derivative hydroxethyl rutosides
- proanthocyanidins, e.g. in grape seed extract

the interstitial fluid which, in turn, bring about proteolysis, thereby reducing the protein-induced chronic inflammatory process which leads to tissue fibrosis
- Inhibition of the synthesis of prostaglandins and leukotrienes, which are inflammatory mediators.

The flavonoids have antioxidant properties inhibiting a number of enzymes, e.g. cyclo-oxygenase and lipoxygenases, leading to a reduction in inflammatory mediators such as prostaglandins and leukotrienes. They also reduce microvascular permeability and capillary filtration rate (Twycross, 2000; Ramelet, 2000). They therefore have similar properties to the coumerols which may potentially be useful in the management of lymphoedema.

Evidence of effectiveness

The Cochrane review (Badger et al, 2003) found 15 randomised controlled trials of benzopyrones in lymphoedema which fitted their criteria (*Table 4*).

The authors felt it was not possible to draw conclusions about the effectiveness of benzopyrones in lymphoedema from the trials reviewed. Some patients may report an improvement in symptoms, e.g. heaviness, tightness or aching but there are concerns about the long-term use of these drugs. Coumarin may cause hepatotoxicity in up to 6% of patients (Loprinzi et al, 1999) who take it and it has been withdrawn in many countries, including the UK. The Cochrane review, therefore, concluded that the current evidence did not support the routine use of benzopyrones in the management of lymphoedema.

Many of the studies reviewed had methodological problems, with small numbers and inconsistent design making it impossible to carry out a meta-analysis. Nevertheless, there were a number of results which suggested that further investigation would be helpful in determining whether particular groups of patients may benefit. For example, in one randomised controlled study of Daflon (Pecking et al, 1997) in 104 women with arm oedema secondary to breast cancer treatment, a subset of 24 patients with severe oedema showed a significant improvement in lymphoscintigraphic parameters in the treatment group.

The only benzopyrone available in the UK is oxerutins. This is a standardised mixture of semisynthetic flavonoids, mainly mono-, di-, tri- and tetra-hydroxyethylrutosides which is licensed for the relief of symptoms of oedema associated with chronic venous insufficiency (BNF, 2007). The studies of this preparation in lymphoedema will be considered in more detail. It should be noted that, as with other benzopyrones, the doses used in lymphoedema are higher than those used in venous disease (Twycross, 2000). The oral bioavailability of oxerutins is 10%.

Although combined physical treatments are now accepted as standard practice internationally (Lymphoedema Framework, 2006), there are still situations where access to services can be difficult... Therefore, an oral medication which can be used to treat lymphoedema without the need for compression garments would be potentially useful.

There were three placebo-controlled trials of oxerutins considered in the Cochrane review (Piller et al, 1988; Taylor et al, 1993; Mortimer et al, 1995). The results related to a total of 81 patients (out of 127 randomised). A comparison of the studies is given in *Table 5*.

These examples illustrate the varied study design, differences in outcome measures and different results typical of studies of benzopyrones in lymphoedema to date. The results do not support the routine use of oxerutins in the management of lymphoedema, combined with physical treatments. However, further high quality trials may help to define a possible role for some groups of patients.

Although combined physical treatments are now accepted as standard practice internationally (Lymphoedema Framework, 2006), there are still situations where access to services can be difficult due to geographical circumstances, or where the climate makes the use of compression garments difficult. Therefore, an oral medication which can be used to treat lymphoedema without the need for compression garments would be potentially very useful. Casley-Smith (1999) suggests that benzopyrones are already proven to be one such treatment, but other reviews (e.g. Badger et al, 2003) find that the evidence is not conclusive.

If benzopyrones do prove to be effective treatments for lymphoedema in some circumstances, it is likely that they will need to be taken over a period of time, and, therefore, there is a need for good data on possible long-term side-effects, particularly with the experience of fatal hepatotoxicity with coumarin (Twycross, 2000). Short-term side-effects of oxerutins include nausea, diarrhoea, pruritus, dizziness and headaches, but these occur with equal frequency as placebo in controlled trials (Twycross, 2000).

A literature search for papers on trials of benzopyrones in lymphoedema since the publication of the Cochrane review (2003) revealed no additional studies. However, Farinola and Piller (2005) have raised the possibility that coumarin hepatotoxicity may be related to cytochrome P450 (CYP2A6) deficiency, such that in poor CYP2A6 metabolisers, coumarin may be metabolised by an alternative cytochrome, CYP3A4, instead, thus producing a cytotoxic metabolite. They advocate the use

of pharmacogenomics to identify patients in whom it may be safe to use coumarin. They also emphasise that the rutosides do not seem to have a hepatotoxic effect like that of coumarin.

Selenium

Selenium is an essential trace element with anti-oxidant properties. It has been investigated as a possible remedy for the side-effects associated with radiotherapy and chemotherapy and also for lymphoedema (Dennert and Horneber, 2006). The mechanisms involved in all of these have been linked to oxidative cell damage and, therefore, theoretically supplementation of selenium intake may be of benefit.

A Cochrane review of selenium for alleviating the side-effects of chemotherapy, radiotherapy and surgery in cancer patients (Dennert and Horneber, 2006) identified one randomised placebo-controlled trial of selenium (sodium selenite orally for 15 weeks) in 60 patients with arm oedema secondary to treatment for breast cancer (Kasseroller, 1998). All patients were also treated with a combination of physical therapies.

During the study period of 15 weeks, there was no evidence of a benefit from selenium in reducing the swelling but no patient in the intervention group developed cellulitis, while 14 patients (50%) in the placebo group did.

The reviewers, however, felt that these results needed to be treated with caution due to a number of methodological issues, e.g. lack of details of outcome assessment, method of diagnosis of cellulitis, details of physical therapy and concurrent drug usage and, therefore, could not be generalised to other populations. They concluded that there was, at present, insufficient evidence on which to make recommendations about selenium supplementation in treating lymphoedema or reducing the incidence of cellulitis in this patient group.

Another Cochrane review of drugs used to reduce the incidence of acute inflammatory episodes (AIEs) in lymphoedema (Badger et al, 2004) considered the same study and came to similar conclusions.

There has also been a suggestion that selenium can reduce head and neck lymphoedema which follows surgery and radiotherapy for head and neck cancer (e.g. Bruns et al, 2003). However, there is again insufficient evidence as yet to make this routine practice.

Diuretics

Loop diuretics, e.g. furosemide are used to treat the oedema of heart failure but are not indicated in pure lymphoedema as they are ineffective (BNF, 2007). It has been argued

Table 4

Benzopyrone trials in the Cochrane review (Badger et al, 2003)

Benzopyrone	Number of trials
Coumarin	7
Oxerutins	3
Coumarin + troxerutin	3
Cyclo 3 Fort (ruscogenin + hesperidin)	1
Daflon (MPFF)	1

(MPFF is micronised purified flavonoid fraction, a semi-synthetic preparation from diosmin; micronisation improves oral bioavailability [Ramelet, 2000])
(Ruscogenin is derived from the plant Butcher's Broom)

Table 5

A comparison of trials of oxerutins in lymphoedema

Feature	Piller et al, 1988	Mortimer et al, 1995	Taylor et al, 1993
Oxerutins dose (per day)	3g	3g	3g
Duration (months)	6	6	6
Design	cross-over (no washout)	parallel group	cross-over (no washout)
Other treatment	nil for one month prior to trial	usual physical treatment	
Site of oedema	arm/leg	arm	arm
Outcome measures	limb volume; skin temperature; tonometry; symptoms	limb volume; symptoms	limb volume; tonometry; symptoms
Results	significant to very significant improvement in all parameters	limb volume stablised (increase in placebo group)	clinically unimportant reduction in limb volume and tissue tone

that in lymphoedema, diuretics may even make the situation worse by increasing the oncotic pressure of the oedema fluid because of an increase in interstitial protein concentration, as a result of reduced water entry through capillary filtration. This, in turn, may exacerbate the formation of fibrosis in the longer term (Földi and Földi, 2003a).

The inappropriate long-term use of diuretics can also lead to secondary hyperaldosteronism which may result in rebound oedema on discontinuation of the diuretic (Földi and Földi, 2003b).

Nevertheless, there are some circumstances, e.g. when a patient with pure lymphoedema experiences an exacerbation of their oedema due to taking a fluid-retaining drug, or when there is an oedema of complex aetiology such as in advanced cancer, when the use of a loop diuretic may be helpful. This should be for as short a time as possible because of the problems described above.

Corticosteroids

In oedema in advanced cancer, there may be a complex aetiology including metastatic lymphadenopathy and extrinsic venous compression due to tumour (Keeley, 2000). If these are present, a trial of a corticosteroid such as dexamethasone may be helpful (Keeley, 2000). The treatment is based upon the concept of steroids reducing peri-tumour oedema, thereby relieving the pressure on lymphatics and/or veins and increasing the flow through them. This may reduce the peripheral oedema.

The evidence for the effectiveness of this approach is anecdotal, but in situations of severe distressing oedema in advanced cancer, it is often appropriate to try it. However, it should be recognised that the corticosteroids themselves may cause fluid retention and exacerbate oedema in longer term use. It is sometimes difficult to determine clinically whether this is occurring, as the oedema may also increase with disease progression. The addition of a diuretic or a reduction in steroid dose may be helpful in discriminating between these two situations.

Pentoxifylline and vitamin E

There is some suggestion that alpha-tocopherol (vitamin E) and pentoxifylline may cause regression of superficial radiation-induced fibrosis. It is possible that these agents may improve arm lymphoedema following radiotherapy for breast cancer (Gothard et al, 2004a).

Gothard et al (2004a) carried out a randomised placebo-controlled trial in 68 women with arm oedema following axillary/supraclavicular radiotherapy and surgery for breast cancer. The women had at least a 20% increase in arm volume and received di-alpha tocopheryl acetate 500mg twice per day orally, plus pentoxifylline 400mg twice per day orally or placebo for six months. The volume of the oedematous limb measured by perometer and expressed as a percentage of the unaffected limb was the primary end-point of the study.

Unfortunately, there was no significant difference in limb volume between the two groups at either six or 12 months of follow-up. Neither was there any difference in tissue fibrosis.

The study thus failed to show any benefit of vitamin E and pentoxifylline in this type of lymphoedema.

Hyperbaric oxygen therapy

Post-radiotherapy fibrosis has in the past been considered to be irreversible. However, recent ideas suggest it is a more dynamic process which may be reversed under certain circumstances (Gothard et al, 2004b). Hyperbaric oxygen promotes healing in bone rendered ischaemic by radiotherapy (osteoradionecrosis) and may also help some soft tissues.

Gothard et al (2004b) reported a non-randomised phase II trial of hyperbaric oxygen in 19 patients with chronic arm lymphoedema and tissue fibrosis after radiotherapy for early breast cancer. The patients underwent 30 treatments of 100% oxygen at 2.4 atmospheres absolute (ATA) for 100 minutes over six weeks. Patients continued with their usual physical treatment for the lymphoedema and no unwanted effects were reported.

The results suggested a clinical effect sufficient to warrant a randomised controlled trial which is currently in progress. They are summarised below:

- 3/19 patients experienced >20% reduction in arm volume at 12 months

Table 6

Side-effects of hyperbaric oxygen therapy

Side-effect	Comments
middle-ear barotrauma (2%)	may require grommets before treatment
'sinus squeeze'	especially with an upper respiratory tract or allergic rhinitis
claustrophobia	
progressive myopia	reversible after treatment finishes in courses of >100 treatments
cataracts	
seizures (0.03%)	

Source: Clark, 2003

- Mean reduction in arm volume at 12 months was 7.5%
- 6/13 patients experienced >25% increase in tracer clearance rate as measured by quantitative lymphoscintigraphy
- 8/15 patients were judged to have reduced induration
- 12/19 patients felt their arms were softer
- 6/19 reported improved shoulder movement.

Potential side-effects from hyperbaric oxygen therapy are given in *Table 6*.

At present, therefore, this is an experimental treatment. Its role in the treatment of post-radiotherapy lymphoedema and whether it has any role at all in other lymphoedemas is yet to be determined.

Conclusions

There is currently insufficient evidence to support the use of benzopyrones, selenium, pentoxifylline and vitamin E in the routine management of lymphoedema. Corticosteroids and diuretics may have a role in the management of specific types of oedema such as that in advanced cancer. JL

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Key points

- Drugs which cause oedema may exacerbate lymphoedema.
- There is currently insufficient evidence to support the routine use of benzopyrones in the management of lymphoedema.
- Corticosteroids and diuretics may have a part to play in managing oedema in advanced cancer.