A systematic review of drug induced ocular reactions in diabetes

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Abstract

***Aims*—To conduct a systematic review of drug induced adverse ocular effects in diabetes to determine if this approach identified any previously unrecognised adverse drug effects; to make a preliminary assessment of the feasibility of this approach in identifying adverse drug reactions; and to assess the current accessibility of this information to prescribing physicians.**

***Methods*—Literature search of online biomedical databases. The search strategy linked eye disorders with adverse drug reactions and diabetes. Source journals were classified as medical, pharmaceutical, diabetes related, or ophthalmological. It was determined whether the reactions identified were recorded in drug datasheets and the *British National Formulary*.**

***Results*—63 references fulfilled the selection criteria, of which 45 were considered to be relevant to the study. The majority of these were case reports but cross sectional surveys, case-control and cohort studies, and review articles were also identified. 61% of the reactions were not recorded in the *British National Formulary* and 41% were not recorded in the datasheets. 55% appeared in specialist ophthalmology journals.**

***Conclusions*—This is a feasible approach to the identification of adverse drug reactions. Adverse reactions not listed in the most commonly used reference sources were found. The majority were published in specialist ophthalmology journals which might not be seen by prescribing physicians.**

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Diabetes is associated with a variety of ocular manifestations and is a major cause of visual impairment.[1 2] Thus, the recognition or anticipation of adverse drug reactions involving the eye is important. However, drug induced ocular side effects are uncommon. Measurements of prevalence are difficult to do and precise estimates are generally unavailable. The data which do exist rely on the astute physician making a connection between an eye condition and the patient's systemic therapy. In the USA, data on all drug induced ocular side effects can be obtained from the National Registry of Drug Induced Ocular Side Effects.[3] It is postulated that, as a result of this registry, ocular adverse effects are identified earlier and patients protected. In the UK, to the authors' knowledge, there is no such equivalent. The Committee on Safety of Medicines (CSM) holds data on all adverse drug reactions, but not specifically on those related to the eye. General physicians must rely on their personal knowledge, official warnings, and the range of journals which they read regularly to help them identify and manage suspected reactions. Two of the most readily accessed information sources are the *British National Formulary* (*BNF*) and the Summary of Product Characteristics (SPCs), formerly known as datasheets.[4 5] However, the possibility that the majority of ocular reactions are reported only in specialist ophthalmology journals reduces the chance of general physicians being aware of some important adverse drug effects.

The purpose of this study was to systematically review the world literature on drug induced ocular side effects in diabetes. Ultimately, a list of drugs and side effects would be produced to aid general physicians in identification of such reactions. This systematic review strategy has not previously been applied to adverse drug reactions and thus a secondary aim was to assess the feasibility of this approach to drug reactions in a clinical area of manageable size. We also wanted to determine whether these adverse reactions were to be found in the standard reference sources—that is, the *BNF* and SPC, and to look at the type of journals where they were reported in order to assess accessibility to this kind of information.

Methods

LITERATURE REVIEW

An online literature search of the databases Medline, Embase, Biosis, Toxline, Pharmline, IOWA, and International Pharmaceutical Abstracts was performed towards the end of June 1998. The search strategy (available from the authors) principally linked eye disorders with adverse drug reactions and was narrowed down by adding the term "diabetes". Criteria for selection of titles produced by the search included the presence of a commonly prescribed drug name and ocular effect in the title. Animal studies were excluded. Titles fulfilling these criteria were downloaded and the full reference obtained where possible. In a small number of cases, for foreign journals, the English abstract was used. If no English translation was available the article was excluded. On scanning the full reference the corresponding author of any article thought to be of value published in the past 10 years was contacted to determine whether they had additional data on similar or other work (published or unpublished). A search of the Cochrane Database

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Table 1 Case reports of drug induced ocular toxicity

Author (year)	*Drug*	*Adverse reaction*	*Population*	*Intervention and outcome*	*Comments*
Miller[13] (1978)	Chlorothiazide	Oculomotor nerve palsy	47 year old male. GTT abnormal on thiazide treatment	7 months of diuretic for nephrolithiasis. 3 days' history of orbital pain and ptosis. Diuretic stopped, 3/12 later, palsy resolved and 2 GTTS were normal	No rechallenge but all other causes of palsy ruled out. Proposed mechanism of glucose intolerance induced microangiopathy
Sponsel[14] (1992)	Indapamide	Bilateral cataracts	39 year old male. Hypertensive and obese	3½ years of indapamide. Hyperglycaemia with reduced visual acuity and colour vision changes. Stopping therapy halted progression of visual disturbances	No rechallenge but no other risk factors for cataracts. Surgery required for cataracts
Wymore[15] (1982)	Chlorpropamide	Optic neuropathy	65 year old male. NIDDM for 1 year	Reduced visual acuity after 1 year of treatment. Dramatic improvement in visual acuity and colour vision on stopping drug	Rechallenge for 5 days showed reduced visual acuity. Vision returned to baseline after stopping
D'Arcy[16] (1989)	Glibenclamide	Myopia	35 year old male	Symptomatic after 2 days of glibenclamide. Vision returned to normal 3 days after discontinuation	No rechallenge. Patient remained on diet control for diabetes
Lightman[17] (1989)	Glyburide (Glibenclamide)	(1) Hyperopia (2) crystalline lens deposits	66 year old male. New case of NIDDM	Osmotic effects thought to be cause of lens changes	No rechallenge. Alternative explanation proposed by Keller[45]
Hamill[18] (1983)	Scopolamine (Transdermal)	Acute angle closure glaucoma	58 year male. NIDDM and hypertensive on methyl dopa and propranolol	Intraocular pressure >80 mm Hg after 4 days of patch treatment. Probably unrelated to diabetes	No rechallenge. Predictable from pharmacology
Sedwick[19] (1992)	Amiodarone	Optic neuropathy	62 year old male. Hypertensive with NIDDM on diazide and glyburide	Sudden visual loss when given amiodarone. Bilateral optic neuropathy	Vision improved after stopping amiodarone. After 3 weeks of rechallenge, vision deteriorated
Zenimaru[20] (1997)*	Interferon	Worsening of retinopathy	38 year old male. Diabetic with hepatitis C	Development of retinopathy with massive vitreous haemorrhages after 9 months	Vitreous haemorrhage required surgery. No rechallenge
Dukar[26] (1993)	OKT_3	Retinal toxicity	Two post-renal transplant females. One had IDDM	Case 1: reduced visual acuity after 1 week of OKT_3. Cataract extraction 2 years later. Repeat OKT_3 resulted in vision loss. Case2: OKT_3 for kidney rejection resulted in total loss in vision after 2nd dose	Rechallenge in case 1. No other reason for vision loss apart from slight narrowing of retinal vessels
Flipovic[21] (1997)*	Ethambutol	Optic neuropathy	Series of cases	Few details available	
Sorensen[22] (1977)	Phenformin + ethanol	Retinal dysfunction	57 year female. Diabetic and obese. Following alcohol binge	Severe reduction in visual acuity. Blindness improved with intensive treatment for lactic acidosis	No rechallenge. Possible mechanism is inhibition of oxidative metabolism
Maddox[23] (1977)	Warfarin	Retinal and vitreous haemorrhages	Female diabetic underwent mitral valvotomy	Given warfarin 11 mg. After 1 year haemorrhaged into both eyes resulting in blindness	No recovery. No rechallenge
Caramelli[24] (1991)	Streptokinase	Retinal and vitreous haemorrhage	46 year old diabetic male with 3 years proliferative retinopathy. Given streptokinase for MI	Marked reduction in vision with some recovery. Cardiac status felt to have benefited from thrombolysis	No rechallenge. Vision improved without further treatment
Jimenez-Lucho[25] (1987)	Isoniazid	Optic neuropathy	71 year old. Also on ethambutol, pyridoxine, nifedipine, and allopurinol	Reduced visual acuity after 7 months of TB treatment. Greatest improvement after stopping isoniazid.	No rechallenge

*Indicates data obtained from abstract.

was also performed.[6] Data from every relevant article were extracted in a systematic format. Data extracted included study type, drug prescribed, details of adverse reaction and population, randomisation, study blindness, inclusion/exclusion criteria, statistical significance and power, follow up, and generalisability. Using this information, a comprehensive list of drugs and their suspected effects on the eye was produced.

JOURNAL CATEGORY

The journal type from all of the articles used in the review were categorised as medical (general or specialist), pharmaceutical, diabetes related, or ophthalmological. The proportion of each type was calculated.

BNF AND SPC AGREEMENT WITH REVIEW LIST

Using the list above, the side effects were crosschecked in the *BNF* and SPC. Each adverse reaction was classified as (A) present in both sources, (B) partial agreement, or (C) present in review list only. Partial agreement was defined as when the *BNF* or SPC contained a phrase which did not precisely define the reaction in question—for example, visual disturbance was in partial agreement with short sightedness.

Results

The electronic search produced a total of 528 titles for further assessment. Sixty three references were identified using the selection criteria, and 45 full references were eventually selected as being relevant to the study. These included four articles available in abstract only and six review articles.[7–12] The majority of studies were case reports (Table 1).[13–26] The other articles consisted of cross sectional, cohort, and case-control studies (Table 2).[27–43]

SUSPECTED DRUG REACTIONS

References were included in the review when the subjects were diabetic or where diabetes was considered to be one of the confounding factors. Despite "diabetes" being one of the search terms, it was sometimes not clear whether the patient groups did include diabetes. For the purposes of the review, this small number of studies was included where the drug reaction was also mentioned by at

Table 2 Drug induced ocular side effects: case-control, cohort, and cross sectional studies

Author (year)	*Study type*	*Drug*	*Adverse reaction*	*Population intervention and outcome*	*Comments*
Lakowski[27] (1977)	Case-control	Oral contraceptive (OC)	Colour vision alteration	14 diabetic women on OC and 20 non-diabetic controls. Age matched. Similar duration of diabetes. All normal vision, nulliparous and no retinopathy. Significant ($p<0.05$) red/green deficiency in diabetic OC users. Subsequent report states main deficiency in yellow/blue areas[44]	Small scale—statistical power not stated. Correlation of deficiency with duration of diabetes
Garg[28] (1993)	Case-control	Oral contraceptive (OC)	Retinopathy	43 cases and controls. Cases all IDDM (15 years+) and on OC 1 year. No change in retinopathy grade over time	Small scale—statistical power not stated. May be biased because studied eye clinic attendees only
Klein[29] (1990)	Cross sectional	Oral contraceptive (OC)	Retinopathy	384 females under age of 40 all with IDDM. full medical and eye exam initially and at 2 years. No relation between OC use and degree of retinopathy. Multiple regression technique	Small scale—statistical power not stated. Bias may have occurred because doctors may not generally prescribe pill to diabetics
Greven[30] (1995)	Cross sectional	Oral contraceptive (OC)	Retinal artery occlusion (RAO)	21 females. Examined all factors likely to be associated with occlusion. 4/21 women on OC. 2/21 had diabetes	No statistical analysis stated
Steinberg[31] (1996)	Cross sectional	Erythropoietin	Hallucinations	18 dialysis patients on erythropoietin with hallucinations. Significant association of hallucinations with diabetic retinopathy and age	Convenience sample of all dialysis patients
Chen[32] (1996)*	Cross sectional	Interferon	Retinopathy	Chronic active hepatitis patients (n=34). 12/34 had retinopathy following interferon which disappeared on cessation of treatment	Authors postulated that mechanism due to inherent vascular abnormalities caused by diabetes
Kawano[33] (1996)	Cross sectional	Interferon	Retinopathy	36/63 hepatitis C patients treated with interferon developed retinal haemorrhages and soft exudates in 4–8 weeks. 14 NIDDMs	Greatest effect in diabetics
Ramamurthy[34] (1997)	Cross sectional	Urokinase	Retinal haemorrhage	20 diabetics on dialysis. Eye examination before and after urokinase	
Isaac[35] (1991)	Retrospective cohort	Phenothiazines	Cataracts	4674 patients with cataracts. Matched for age and sex. Used conditional logistic regression. Relative incidence of cataract was 3.5 higher in phenothiazine users of 3–5 years' duration	Also found steroids and benzodiazepines increased risk of cataract
Clair[36] (1989)	Case-control	Allopurinol	Cataracts	From pharmacy records of allopurinol users. 51 cases and 76 controls. Confounders age, sex, diabetes, and hypertension ruled out by logistic regression. Risk ration for cataract of 1.3 not significant	Potential bias in controls. Selection based on response to offer of free eye test, over 80% refused. Cases all had previous eye examinations
Liu[37] (1991)	Cross sectional	Allopurinol	"Lens changes"	53 gout patients from gout clinic. All on 300 mg daily for at least 18 months. High prevalence (25%) of thinning of clear zone of lens. 12% with cataracts	Background incidence not stated. No statistical analysis
Leske[38] (1991)	Case-control	Allopurinol Oral steroids	Cataracts (various types)	945 cases, 435 controls in eye hospital. Investigated nutrition, medical history, and other risk factors. Logistic regression gave adjusted ORs of 1.56, diabetes; 5.83, oral steroids; 2.48, allopurinol	"Lens opacities case control study". Major study
Davis[39] (1997)	Cross sectional	Cidofovir	Iritis and hypotonia	Of 43 patients with CMV retinitis, 26% developed iritis. Impaired visual acuity occurred in 5 eyes	Iritis more likely to occur in diabetics ($p<0.05$)
Pfefferman[40] (1977)	Cross sectional	Prednisolone	Cataracts	78 renal transplant patients. 2/78 with severe diabetic retinopathy. 20 controls. Correlation of cumulative prednisolone dose with cataracts. No statistics	Haemodialysis duration, age, and daily prednisolone dose not correlated with cataract
Cumming[41] (1997)	Cross sectional	Inhaled steroids	Cataracts	3654 volunteers. Assessed diabetes, hypertension, inhaled and oral steroid use. Groups similar for sex, smoking, and diabetes. Ordinal regression gave adjusted ors of 1.8	Some missing data on steroid usage and confounders
Garbe[42] (1997)	Case-control	Oral glucocorticoids	Open angle glaucoma and ocular hypertension	Elderly population. 9793 cases on treatment. 38 325 controls—randomly selected eye patients. Logistic regression adjusted for various confounders including diabetes. Adjusted odds ratio was 1.41 for current users of steroids for either glaucoma or ocular hypertension	Weak association but significant. Authors suggest regular IOP monitoring required in elderly on long term steroids
Yablonski[43] (1978)	Intervention study	Dexamethasone (topical)	Cataracts	11 diabetics. One eye treated with 0.1% eye drops. 9 showed pathology (4 requiring surgery) in treated eyes. 1 patient developed cataracts in untreated eye	Difference was significant ($p<0.005$)

*Indicates data obtained from abstract.

Table 3 Summary of reported drug induced ocular reactions

Drug	*Reaction*	*Comments*
amiodarone	optic neuropathy	sudden visual loss
chlorothiazide	oculomotor nerve palsy	
indapamide	cataract	bilateral
chlorpropamide	optic neuropathy	visual loss
glibenclamide	(1) myopia, (2) hyperopia, (3) lens changes	vision returned to normal on stopping therapy
interferon	retinopathy	mostly asymptomatic
streptokinase	retinal/vitreous haemorrhage	marked reduction in vision
warfarin	vitreous haemorrhage	blindness
erythropoietin	visual hallucinations	mechanism uncertain
isoniazid	optic neuropathy	vision normalised after stopping
ethambutol	optic neuropathy	
phenformin + ethanol	blindness	secondary to lactic acidosis following drinking binge
oral contraceptive	(1) diabetic retinopathy, (2) colour vision disturbance	(1) no adverse effect (2) mechanism uncertain
phenothiazines	cataracts	large study–strong association
allopurinol	cataracts	risk independent of diabetes in one study but significant factor in another
cidofovir	iritis + hypotony	iritis more likely in diabetes
scopolamine	acute angle glaucoma	predictable from transdermal patch
steroids (oral)	open angle glaucoma and ocular hypertension	large study confirmed increased risk
steroids (oral)	cataracts	increased risk
steroids (eye drops)	cataracts	small study but significant risk
steroids (inhaled)	cataracts	increased risk
OKT_3	reduced visual acuity	uncertain mechanism

least one other study which did include diabetes as above. Table 3 summarises the reactions obtained, listed according to drug or drug group. In addition, the review articles mentioned a number of side effects not specifically occurring in diabetes and included reduced visual acuity with cisplatin and cytarabine, papilloedema with ketoconazole, and retinopathy with chloroquine.[8 10]

JOURNAL TYPE

Of the 45 relevant journals, seven (15.6%) were specialist medical, 11 (24.4%) were general medical, 25 (55.6%) were ophthalmological, with one (2.2%) pharmaceutical and one (2.2%) diabetes related journals. Thus, over half of the journals would, most probably, be read by ophthalmologists only.

BNF SPC CROSS REFERENCING

Table 4 displays the results of the cross check between the drug list and the *BNF*/SPC. Fewer side effects were reported for the datasheet because certain products were not listed in the SPC. OKT_3 was not listed in either the *BNF* or SPC.

Discussion

This literature search identified studies of all types. These are discussed in relation to ocular structure affected.

RETINA

Cross sectional studies suggested that oral contraceptive pill use does not have any effect on diabetic retinopathy.[28 29] Interferon treatment for hepatitis C, however, does cause retinopathy. Several case reports were identified documenting this. The funduscopic appearances have some features in common with diabetic retinopathy suggesting that interferon retinopathy is also the result of a microangiopathy.[32] The suggestion was made that the retinopathy was worse in patients with diabetes. This was found to be statistically significant in another study of 63 patients with hepatitis treated with interferon where 11/12 (92%) of patients with diabetes developed evidence of retinopathy although it was asymptomatic in the majority.[33] Treatment with intravenous cidofovir for cytomegalovirus retinitis caused iritis in 26% of 43 patients.[39] The risk of iritis appeared to be increased in patients with diabetes.

Lakowski and Morton describe colour vision changes that occur with diabetes and also with oral oestrogen usage.[27 44] Steinberg *et al* described visual hallucinations in dialysis patients after erythropoietin.[31] Risk factors for hallucinations on this treatment included diabetic retinopathy or cataracts. Inhibition of oxidative metabolism in the retina was thought to be responsible for blindness which occurred in a diabetic patient with lactic acidosis following phenformin treatment.[46]

LENS AND PUPIL

The effects of glucocorticoids on the eye were examined in a number of studies. Risk of cataract was examined in a large matched cohort study by Isaac *et al* who found that risk was increased with use of systemic steroids, phenothiazines, antidiabetic agents, and benzodiazepines.[35] It has recently been claimed that use of inhaled steroids is associated with the development of cataracts.[12 41] Topical dexamethasone eye drops appear to cause cataracts.[43] The relation between cataract and allopurinol use has also been examined. Studies by Liu *et al* and Leske *et al* did find a relation while in the study by Clair *et al* no significant increase in

Table 4 Comparison of side effects obtained from literature search with those found in BNF and datasheet

Category	*Number in BNF (%)*	*Number in SPC (datasheet) (%)*
A, complete agreement	6 (26)	10 (45)
B, partial agreement	3 (13)	3 (14)
C, present in literature review list but not in *BNF*/datasheet	14 (61)	9 (41)
Totals	23 (100)	22 (100)

odds ratio was observed.[36–38] The presence of diabetes appears to increase the risk.

Lightman *et al* suggested that the modern, more potent sulphonylureas cause changes within the lens altering refraction.[17] This phenomenon has previously been described by Keller.[45] Hyperglycaemia in diabetes results in sorbitol accumulation in the lens, along with other diabetes specific metabolic changes at the cellular level. D'Arcy reported a single case of glibenclamide induced accommodation paralysis and cited older references to sulphonylurea induced myopia.[16] It is suggested that there is swelling of the lens and ciliary body with forward displacement of the lens-iris diaphragm. Topical ophthalmic and oral glucocorticoids may cause glaucoma.[42]

The effect of pupillary dilatation on visual acuity is important in relation to driving. It is now policy in most diabetes units that diabetic patients should undergo mydriasis before funduscopy. Tropicamide is generally used for its short duration of action, but despite this a recent study has shown that a minority of patients have binocular visual acuity insufficient to meet the legal requirement for driving 1 hour after mydriasis.[47] Thus patients should now be advised (usually at the previous visit) not to drive themselves after mydriasis. The risk of precipitating acute glaucoma is considered small enough to be acceptable. Of the various possible adverse outcomes of pupil dilatation, recent experience is that the alternative—missing sight threatening retinopathy—carries the greatest medicolegal risk.

OPTIC NERVE

Wymore and Carter described a case of optic neuropathy with chlorpropamide which recovered with withdrawal of the drug and cited two other examples from the literature.[15] This adverse effect is not mentioned in the *BNF*. Elsewhere, Sedwick discusses the possible relation between amiodarone induced and ischaemic optic neuropathy in a diabetic patient.[19] Optic neuropathy is well recognised with ethambutol. The search identified a diabetic patient with tuberculosis in whom isoniazid was thought to be the predominant factor.[25] These authors cite 13 other cases of optic neuropathy due to isoniazid.

VITREOUS

Several reports described vitreous haemorrhage in patients given warfarin, streptokinase, or recombinant tPA.[23 24] Since these treatments are commonly used, generally without detailed retinal assessment, this adverse effect is likely to be substantially more common than generally realised. Physicians perhaps do not always appreciate that haemorrhage can occur despite laser treatment if the new vessels have not fully regressed. One report described bilateral vitreous haemorrhage requiring vitrectomy in a non-diabetic patient following tPA.[48] There is evidence that aspirin is not contraindicated in diabetic patients with proliferative retinopathy.[7]

RETINAL ARTERY AND VEIN

Greven *et al* described retinal artery occlusions in 21 patients under the age of 40.[30] The majority had one or more risk factors, two had diabetes, and five were taking oral contraceptive agents.

Diabetes is a risk factor for retinal vein occlusion (RVO).[49] Kirwan *et al* found an associaton between oral contraceptive use and RVO in women aged under 35.[50] Hormone replacement therapy with lower doses of oestrogens did not appear to be a risk factor. They concluded that RVO is a contraindication to use of oral contraception.

GENERAL CONCLUSION

Of particular interest was whether our approach would identify new adverse reactions. This was likely to come from individual case reports. Single examples must be considered unconfirmed. For example, the potential for thiazide treatment to cause oculomotor palsy and cataracts has not been reported elsewhere.[13 14] However, chlorpropamide optic neuropathy and lens changes due to second generation sulphonylureas both appeared in more than one report but do not seem to have made it into the reference works. Such reports are by their nature anecdotal but the prevalence of such reactions is likely to be higher than realised. Thus a system of prospective surveillance is needed.

INFORMATION AVAILABILITY

To estimate how much of this information is readily available to physicians we determined how many of them were listed in the *BNF* and the data sheets. From Table 4, the data sheets were slightly more accurate than the *BNF* with 45% and 26% respectively in complete agreement with the literature review list. This is not surprising because the datasheet, which outlines the licensed indications for a specific drug, is generally much more detailed than the equivalent *BNF* entry. The most striking result is that between 41% and 61% of the side effects from the review were not present in the *BNF* or datasheet. It is uncertain whether this reflects lack of awareness of the report or delay before new side effects are included, or an editorial opinion that the associations between drug and effect was not strong enough to merit inclusion.

Approximately one quarter of all reactions were reported in general medical journals. This means that 75% of the reactions would be unlikely to be read by physicians who are responsible for prescribing the majority of these drugs. Although the reactions cited in Table 3 are mostly rare, unless the general population of prescribers are made aware of these suspicions, their true incidence may never be known. One possible solution is to ensure that the *BNF* should include more of these reactions. However, as discussed above, this is not without its problems. There is a need, therefore, for an early warning system where prescribers can share their experiences of potential ocular reactions. Perhaps the first stage of this process should involve the setting

up of a UK registry of drug induced ocular side effects.

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