hole formation. The mechanism of hole formation may be multi-factorial, and may be initiated by any of the following:

(1) an increase in vitreomacular traction caused by macular oedema;
(2) an increase in tangential vitreous traction, such as in idiopathic hole;
(3) iatrogenic intraoperative tugging, and
(4) the development of a preretinal macular fibrotic membrane following vitrectomy (Brazitikos & Stangos 1999).

In this case, macular hole was not observed preoperatively, as the preoperative OCT shows (except for a small subfoveal serous elevation), or intraoperatively. Although the exact timing of hole formation could not be established in this case, neither intraoperative tugging nor postoperative premacular fibrosis are likely to represent the mechanism for hole formation. Rather, pre-existing macular oedema, which can develop in a diabetes patient during the early post-vitrectomy period, may have resulted in macular hole formation.

The possibility of spontaneous closure cannot be excluded, as has been noted in some previous reports (Kokame & McCauley 2002; Lo & Hubbard 2006). However, it is unlikely to have occurred in our case because the macular hole persisted at 1 week prior to IVTA. Consistent with the theory that macular oedema may be an inciting factor that modifies foveal anatomy, leading to hole formation, the fact that the hole closed 2 weeks following IVTA in our case strongly supports the suggestion that IVTA plays a role in macular hole closure. A recent report on IVTA proposed that the treatment encouraged macular hole formation by causing thinning of the inner retina (Lecleire-Collet et al. 2007). However, Halkiadakis et al. (2003) demonstrated the closure of a full-thickness macular hole associated with uveitic macular oedema after peribulbar triamcinolone injection.

In conclusion, inflammation and macular oedema might be causative factors in macular hole formation in patients with diabetic retinopathy. The present case indicates that the treatment of macular oedema with IVTA may lead to macular hole closure.

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Mean standard deviations for common glaucoma treatments

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Editor,

Proper sample size calculation is vital to statistically accept or reject a difference between analysed treatment groups in a prospective clinical trial. In regulatory and post-marketing glaucoma trials using a parallel design, a standard deviation (SD) for the mean intraocular pressure of 3.5 mmHg (Goldberg et al. 2001; Netland et al. 2001; Chew et al. 2004) for individual treatment arms (to detect a 1.5 mmHg difference between medications) is commonly used.

However, little previous literature has reviewed the SD used for individual treatment groups in glaucoma trials to determine if this level is appropriate. The purpose of this study was to review past clinical trials to determine the SD for treatment groups generally, and among individual classes of medicines.

We included in this analysis 17 articles published between January 1995 and May 2007, which contained 6252 treated ocular hypertension or open-angle glaucoma patients from 45 treatment arms using 14 different treatment regimens (Alm & Stjernschantz 1995; Strahlman et al. 1995; Schuman 1996; Watson & Stjernschantz 1996; Boyle et al. 1998; Clineschmidt et al. 1998; Strohmaier et al. 1998; Watson 1998; O'Donoghue 2000; Kampik et al. 2002; Parrish et al. 2003; Shin et al. 2004; Barnebey et al. 2005; Camras & Sheu 2005; Hughes et al. 2005; Diestelhorst & Larsson 2006; Holló et al. 2006). All articles were identified online at http://www.pubmed.com and were multi-centred, single- or double-masked, randomized, Phase III or IV studies that included at least 80 enrolled patients per treatment arm of current commonly used glaucoma preparations. The studies must have measured the pressure by Goldmann applanation tonometry over at least three daytime time-points (diurnal curve). Articles included in this analysis were those that met the inclusion criteria, and whose data could be collected from the online abstract or from the full articles owned by the research site (PRN). All qualified and available articles were included. Statistical analyses were performed with the random effects model.

The mean SDs for the diurnal curve of individual treatment groups are

Table 1. Mean standard deviation (SD) for the diurnal curve analysed by medicine in this study.

Medicine	Treatment arms	Patients	SD
Latanoprost	8	1028	2.7
Bimatoprost	1	136	2.8
Travoprost	2	222	3.4
Timolol	9	1199	3.5
Brimonidine	3	804	3.8
Dorzolamide	5	675	4.5
Betaxolol	1	107	5.4
Travoprost and timolol	2	237	2.9
Travoprost and brinzolamide	1	97	3.0
Latanoprost/timolol fixed combination	2	380	3.1
Travoprost/timolol fixed combination	2	233	3.1
Latanoprost and timolol	1	247	3.1
Dorzolamide and timolol	2	231	3.8
Dorzolamide/timolol fixed combination	6	656	3.9

shown in Table 1. The mean SD among all treatment groups was 3.5 mmHg (range 2.7–5.4 mmHg). Monotherapy treatment groups had a mean SD of 3.7 mmHg. There was a statistical difference in the SD among individual monotherapy treatments, with latanoprost and bimatoprost having the lowest ($P = 0.0011$).

In contrast, the adjunctive treatments had a mean SD of 3.3 mmHg. A statistical difference also existed among individual treatments, with the prostaglandin based combinations having the lowest ($P = 0.036$). However, no statistical difference existed in the mean SD between all monotherapy and adjunctive therapy studies ($P = 0.27$).

The results of this meta-analysis help confirm the use of 3.5 mmHg to size large, multi-centre, parallel trials for glaucoma. This information should provide greater confidence in designing glaucoma trials to academic or pharmaceutical scientists.

This analysis also showed that either mono- or adjunctive therapy trials that include prostaglandin analogs generally have lower SDs. Consequently, these data could be used to adjust the sample size in planning future Phase IV trials. Potentially, the use of lower SDs could reduce the sample size and trial costs. In contrast, medicines that generally demonstrate a shorter-term efficacy and greater peak/trough differences, such as brimonidine and dorzolamide, showed higher SDs.

This analysis suggests that an SD of 3.5 mmHg generally reflects accurately the distribution of the intraocular pressure in ocular hypertension and open-angle glaucoma patients included in parallel designed clinical trials.

This analysis did not take into account the number of patients required to determine safety in the development of a new medication, only to determine efficacy. Clinical trial planning should also consider an adequate number of patients to reflect the safety profile of the new medicine.

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Gemcitabine-induced retinopathy in a diabetic patient

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Editor,

Gemcitabicine, a nucleoside analogue, has been approved for the treatment of a variety of cancers (bladder, ovarian, pancreatic, etc). The major dose-limiting side-effect seems to be myelosuppression (Noble & Goa 1997). We report the case of a 58-year-old white man suffering from a bladder carcinoma who developed a retinal microangiopathy after being treated with gemcitabine (Gemzar®, Lilly, France).

The patient was given a combination of gemcitabine and a platinium salt after surgical management from March to June 2006 with good response. Past medical history included insulin-dependent diabetes and hypertension, which were well controlled.

In July 2006, visual acuity decreased to 20/40 in both eyes after four cycles of chemotherapy. Dilated fundus examination showed mild retinal oedema associated with cotton-wool spots and haemorrhages in both eyes (Fig. 1A). Fluorescein angiogram demonstrated microaneurysms, and capillary vascular leakage (Fig. 1D). Optical coherence tomography (OCT) revealed thickening of the macula [right eye (OD) = 319 μm; left eye (OS) = 282 μm] and of the retinal nerve fibre layer (RNFL) of both eyes (OD = 133.48 μm; OS = 126.31 μm) (not shown). Retinopathy induced by chemotherapy was diagnosed. Gemtabicine was discontinued and carboplatine was maintained.

In August 2006, visual acuity improved to 20/25 OD and 20/30 OS. Fluorescein angiogram showed resolution of vascular leakage and persistence of microaneurysms (Fig. 1E). Macular and RNFL thickness decreased on OCT. A follow-up retinal examination in September showed that retinopathy had improved and cotton-wool spots and haemorrhages had mostly reabsorbed (Fig. 1B).

The patient remained asymptomatic and was monitored every 4 weeks until his bladder cancer relapsed in February 2007. Reintroduction of gemcitabine was attempted. One month later, retinopathy appeared with cotton-wool spots, intraretinal haemorrhages (Fig. 1C) and mild vascular leakage on fluorescein angiogram without change in visual acuity (Fig. 1F). Discontinuation of gemcitabine was decided and the patient died 4 months later.

Retinal changes found in this case included aneurysms, cotton-wool spots, intraretinal haemorrhages and vascular leakage on fluorescein angiogram. Clinical improvement after gemcitabine withdrawal and relapse of retinopathy from re-exposure to the drug strongly suggest gemtabicine to be causative for the retinopathy.

The retinopathy occurs within 1 month at reintroduction of gemcitabine and may be asymptomatic. Our patient presented decreased vision caused by macular involvement (haemorrhages, oedema) after four cycles of chemotherapy when he was first treated, and retinopathy appeared without vision change when gemcitabine was reintroduced. The prognosis is good with resolution of retinal changes after gemcitabine discontinuation.

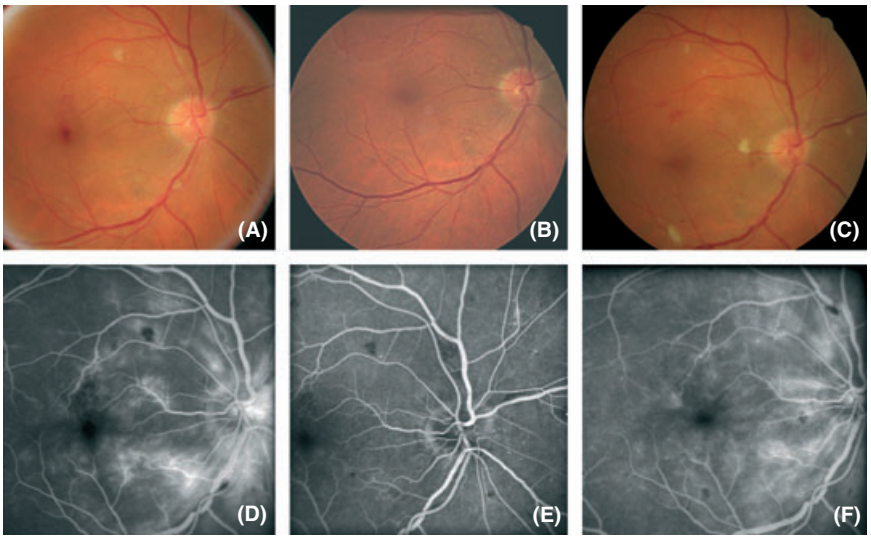

Fig. 1. Gemcitabine-induced retinopathy of the right eyes after four cycles of chemotherapy with cotton-wool spots, intraretinal haemorrhages and microaneurysms (A) and capillary vascular leakage at late phase of fluorescein angiogram (D). One month after discontinuation of gemcitabine, cotton-wool spots and haemorrhages have mostly reabsorbed (B). Late phase of fluorescein angiogram showed persistence of microaneurysms and resolution of vascular leakage (E). Retinopathy reappeared one month after re-exposure to gemcitabine with cotton-wool spots, intraretinal haemorrhages (C) and capillary vascular leakage (F).