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Predictive value of the efficacy of glaucoma medications in animal models: preclinical to regulatory studies

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ABSTRACT

To gain regulatory approval for a new medicine, a pharmaceutical company must take the new product through a series of clinical trials (Phases I–III). Animal models are important in the new drug-development process because they allow for the testing of the efficacy and safety of potential new medicines in a cost-efficient manner that avoids the risk of serious adverse events to humans. Unfortunately, there is no perfect animal treatment model for glaucoma. Animal studies hopefully predict the results of clinical studies, but with estimating efficacy, the limited size and duration of these studies, as well as the animal model selection, might restrict the ability to accurately predict future results. There is little information which compares various available animal models and how well these preclinical studies predict the efficacy of a new product in clinical trials. The purpose of this review article is to analyse animal model studies evaluating potential glaucoma products and determine parameters associated with commercial availability. We discuss how animal models provide some success in predicting commercial launch of a new glaucoma medicine, especially the hypertensive and monkey models, but highlight that caution must be used in interpreting individual models or studies.

INTRODUCTION

To gain regulatory approval for a new medicine, a pharmaceutical company must take the new product through a series of clinical trials (Phases I–III). These trials typically provide the most relevant information on the efficacy and safety of the new product on which regulatory approval is based. However, such studies are expensive in both money and personnel use. Therefore, a decision whether to proceed to clinical trials generally is made by a pharmaceutical company, in conjunction with the appropriate regulatory agency, based on the results from preclinical animal model studies for both efficacy and safety.

Consequently, adequately performed animal studies hopefully predict the results of clinical studies. However, especially for estimating efficacy, the limited size and duration of these studies, as well as the animal model selection, might restrict the ability to accurately predict future results. Unfortunately, there is little information which compares various available animal models and how well these preclinical studies predict the efficacy of a new product in clinical trials.

The purpose of this analysis was to review animal model studies evaluating potential new glaucoma products and determine parameters associated with commercial availability.

MATERIALS AND METHODS

Inclusion/exclusion criteria

We performed this study using published literature on Pubmed (http://www.ncbi.nlm.nih.gov/entrez/query) and the personal database of glaucoma literature of one of the authors (WCS). We used the generic and brand name of each commercially available medicine as keywords along with the term 'glaucoma.' Also, we searched under each specific animal type and glaucoma (eg, 'animal model glaucoma,' 'rabbit model glaucoma').

We included the preclinical studies using animal models since 1977 for glaucoma medicines that are currently commercially available and commonly used as well as earlier molecules noted to be effective with poor side-effect profiles, in the USA and Europe.[1] We also included animal-model studies of medicines which did not become commercially available or were noted to be ineffective as a control group.[2] We did not include medicines after 2005 because insufficient time had passed to determine if they had not received regulatory approval for commercial sale. We assumed, unless otherwise published, for the purpose of this article that the drug sponsors had discontinued development owing to a lack of efficacy. Any drug known to be not developed for safety concerns was excluded from the analysis.

We excluded articles that evaluated non-glaucoma medicines and that included human subjects. For commercially available classes of medicines, we excluded concentrations within >50% higher or lower than the marketed product. For non-commercially available medicines, we excluded articles published after 2005 because of the possibility that they may yet undergo clinical development. Excluded also were studies that had insufficient peak or diurnal curve data that showed the pressure returning to baseline (<1 mm Hg). All identified articles that met the inclusion/exclusion criteria were used for this review.

Procedures

Owing to the design of this study, an informed consent form and clinical trial registration were not applicable. We extracted from each animal study article the following information: literature reference, medicine evaluated, medication class, animal

model type, if it was a hyper- or normotensive model and means of raising the pressure if appropriate, number of treatment arms as well as the baseline, peak and diurnal (6 h) pressure. The percentage peak (and range) and percentage diurnal (and range) intraocular pressure and reduction were calculated from the provided data. The diurnal pressure decrease was determined by either the value provided in the article or a figure in the paper at each time point provided over the first 6 h within the article itself down to every 1 h frequency. Only a 6 h diurnal was used because with a longer period of diurnal reduction, the length of time the pressure is reduced in an animal model is often less than in the human.[3] Studies were included that did not have a 6 h time point measured, but the pressure had returned to baseline prior to 6 h. Therefore, a 0% reduction at hour 6 was assumed. The last treatment day was used for all analysis. No attempt was made to evaluate safety.

Statistics

In this study we described the animal model results divided by medications commercially available and unavailable by mean diurnal and peak pressures (with the range of pressures if multiple treatment arms were evaluated). We then further described the results in the following ways: first, by class of medicine; second, by individual animal model; third, by hyper- versus normotensive models; and fourth, by animal models thought effective in evaluating specific medicine classes to non-specific models associated with no distinct class of medicine.

A one-way ANOVA was used to analyse mean percentage intraocular pressure reductions between groups.[4] All tests were two-way, and a p value of 0.05 was used to declare significance.

RESULTS

Included articles

The initial review for this study identified 128 articles that could potentially be included. However, 80 were excluded because peak and diurnal pressures could not be determined due to the articles lacking baseline values or up to the 6 h postdosing pressures.

This study evaluated 19 classes of medicines in 114 treatment arms studying six different animal models for glaucoma from 48 articles available in the literature by the inclusion/exclusion criteria.[5–52]

Current glaucoma medicines and predicting commercial availability

Current glaucoma preparations which have become commercially available and their associated published animal studies by pharmacological class are shown in table 1. The diurnal pressure reduction across all animal studies was 19% (range −17 to 92%) and the peak decrease 26% (range −5 to 92%).

Commercially unavailable medicines

Glaucoma preparations which have not yet become commercially available are shown in table 2. The diurnal pressure reduction was 16% (range −7 to 64%) and a peak decrease of 24% (range 4 to 66%).

Animal model performance: general

Table 3 summarises individual animal models from tables 1 and 2 and their diurnal and peak intraocular pressure reduction separated between medications that became commercially available or not. No difference generally was observed in the percentage diurnal or peak pressure decrease between those

Table 1 Commercially available glaucoma medications: percentage mean (percentage range)

Class	Medicine	Model	Induction	Eyes	Treatment arms	Diurnal intraocular pressure reduction	Peak intraocular pressure reduction
Alpha and beta-agonist	Epinephrine	Monkeys	Laser	16	2	29 (27 to 31)	28 (24 to 31)
		Rabbits	None	16	2	3 (0 to 5)	20 (16 to 24)
			aCT	5	1	36	52
Alpha-agonist	Brimonidine, apraclonidine, clonidine	Rabbits	None	80	4	0 (−10 to 13)	14 (−5 to 25)
		Monkeys	None	6	1	17	44
			Laser	8	1	75	80
Beta-antagonist	Betaxolol	Rats	Constant light	6	1	10	12
			None	6	1	24	27
Beta-blockers	Timolol	Rabbits	None	62	6	13 (−17 to 92)	24 (2 to 92)
			Laser	12	1	20	23
			aCT	6	1	13	18
		Monkeys	Laser	16	2	37 (32 to 42)	39 (33 to 45)
		Cats	None	28	2	19 (17 to 21)	23 (17 to 29)
		Dogs	None	11	1	27	27
Carbonic anhydrase inhibitor	Dorzolamide	Monkeys	Laser	8	1	24	33
			None	8	1	18	19
		Rabbits	aCT	6	1	29	33
Cholinergic agonist	Pilocarpine	Rabbits	Laser	24	2	18 (0 to 35)	24 (13 to 35)
			None	16	2	1 (0 to 2)	7 (4 to 10)
		Dogs	None	20	2	15 (10 to 19)	22 (15 to 28)
		Monkeys	Laser	16	2	44 (31 to 57)	46 (34 to 57)
		Cats	None	10	1	16	29
Prostaglandins	Latanoprost, travoprost, bimatoprost, tafluprost, PGF_2alpha, PGF_2alpha ester	Monkey	Laser	40	7	14 (6 to 23)	16 (8 to 26)
			None	14	2	25 (23 to 26)	32 (29 to 35)
		Mice	None	28	4	16 (13 to 18)	22 (19 to 24)
		Rabbits	None	16	2	26 (25 to 26)	32 (30 to 33)
		Dogs	None	6	1	39	63

aCT, alpha-chymotrypsin induction; PG, prostaglandin.

Table 2 Commercially unavailable glaucoma medications: percentage mean (percentage range)

Class	Medicine	Model	Induction	Eyes	Treatment arms	Diurnal intraocular pressure reduction	Peak intraocular pressure reduction
Alpha-agonist	Corynanthine, B-HT 920, 5-methyl-urapidil, oxymetazoline, nylidrin	Monkeys	Laser	40	5	21 (0 to 50)	32 (16 to 66)
			None	36	4	4 (−3 to 9)	15 (11 to 18)
		Rabbits	None	16	2	6 (−3 to 14)	27 (26-28)
Alpha-antagonist	Prazosin	Rabbits	None	10	1	−7	22
Beta-agonist	Prenalterol, salbutamol	Cats	None	16	2	21 (12 to 29)	31 (22 to 40)
Beta-antagonist	Atenolol, H 35/25	Cats	None	16	2	11 (6 to 16)	17 (8 to 26)
Carbonic anhydrase inhibitor	MK-927, trifluormethazolamide	Monkeys	Laser	14	2	22 (20 to 23)	32 (26 to 38)
		Dogs	None	6	1	27	25
		Rabbits	None	12	1	−1	12
Calcium-channel blocker	Flunarizine	Rabbits	None	15	1	11	16
Cyclic adenosine 3′,5′-cyclic monophosphate activator	Forskolin	Monkeys	Laser	16	2	8 (2 to 13)	13 (10 to 16)
			None	20	1	11	20
		Rabbits	Laser	12	1	23	23
			None	52	3	15 (13 to 16)	22 (19 to 26)
Cannabinoid receptor agonist	WIN 55212-2	Monkeys	None	23	4	12 (4 to 16)	18 (8 to 26)
Ergot alkaloids	Pergolide	Monkeys	Laser	10	1	26	27
			None	12	1	19	19
Macrolide	Latrunculin B	Monkeys	None	8	1	12	16
MT3 receptor agonist	5-methoxycarbonylamino-N-acetyltryptamine	Monkeys	Laser	8	1	1	9
Nitric oxide synthase inhibitor	Nitro-L-arginine methyl ester	Rabbits	Alpha-chymotrypsin induction	12	3	6 (1 to 10)	23 (4 to 44)
Prostaglandins	PGA_2, PGA_2 ester, PGA_2-isopropyl ester, PGE_2, 8-iso PGE_2	Monkeys	Laser	32	4	18 (13 to 27)	21 (17 to 28)
			None	10	2	15 (10 to 19)	20 (18 to 22)
		Rabbits	None	32	4	26 (17 to 35)	32 (26 to 47)
		Dogs	None	10	2	59 (54 to 64)	61 (57 to 64)
Protein phosphatase inhibitor	Vanadate	Monkeys	Laser	16	2	12 (9 to 15)	17 (12 to 21)
			None	8	1	6	8
		Rabbits	None	24	2	23	31 (27 to 34)
Rho kinase inhibitor	H-7, Y-23762	Monkeys	Laser	8	1	−3	8
			None	7	1	13	24
		Rabbits	None	18	2	26 (16 to 35)	46 (35 to 57)

PG, prostaglandin.

animal models that evaluated commercially available medicines or those that failed to be commercialised.

Figure 1 shows the diurnal pressure reduction for all models separated by products that were successfully commercialised or not. A 15% reduction in pressure identified the maximum number of future commercialised or non-commercialised products (~55% each).

Animal model performance: specific types

In the four animal types that had direct comparative data between products that were commercialised successfully or not, there was no greater decrease in diurnal and peak pressures in commercialised medicines in cats, dogs and rabbit studies. However, there was a greater decrease in diurnal and peak pressures in commercialised than in failed medications in the monkey model.

Animal model performance: hyper- and normotensive

Table 3 also shows animal models which included natural or induced pressure elevation and normotensive models. There was a difference observed in hypertensive models in commercially available, compared with non-commercialised, medicines, with diurnal IOP, but not with peak IOP. Importantly, there was no difference in the mean baseline pressure between studies that

Table 3 Commercially available and unavailable glaucoma medications by animal model and induction type: percentage mean (percentage range)

	Commercial medications			Non-commercialised medications				
Animal type	Treatment arms	Diurnal IOP reduction	Peak IOP reduction	Treatment arms	Diurnal IOP reduction	Peak IOP reduction	Diurnal p value	Peak p value
Animal model							0.32	0.56
Cats	3	18 (16 to 21)	25 (17 to 29)	4	16 (6 to 29)	24 (8 to 40)	0.72	0.91
Dogs	4	24 (10 to 39)	33 (15 to 63)	3	48 (27 to 64)	49 (25 to 64)	0.09	0.38
Mice	4	16 (13 to 18)	22 (19 to 24)	NA			NA	
Monkeys	19	26 (6 to 75)	30 (8 to 80)	33	13 (−3 to 50)	20 (8 to 66)	0.001	0.013
Rabbits	22	12 (−17 to 92)	22 (−5 to 92)	20	15 (−7 to 35)	27 (4 to 57)	0.63	0.34
Rats	2	17 (10 to 24)	20 (12 to 27)	NA			NA	
Glaucoma induction								
Hypertensive	22	26 (0 to 75)	29 (8 to 80)	23	15 (−3 to 50)	23 (4 to 66)	0.02	0.21
Normotensive	32	14 (−17 to 92)	24 (−5 to 92)	37	16 (−7 to 64)	25 (8 to 64)	0.60	0.75

IOP, intraocular pressure.

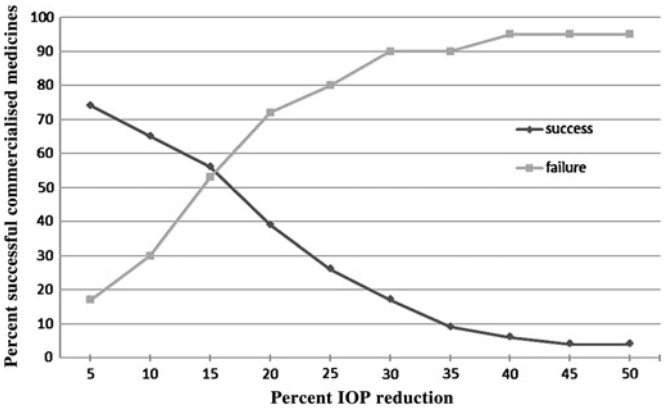

Figure 1 Diurnal pressure reduction for all animal models separated by products that were successfully commercialised or not.

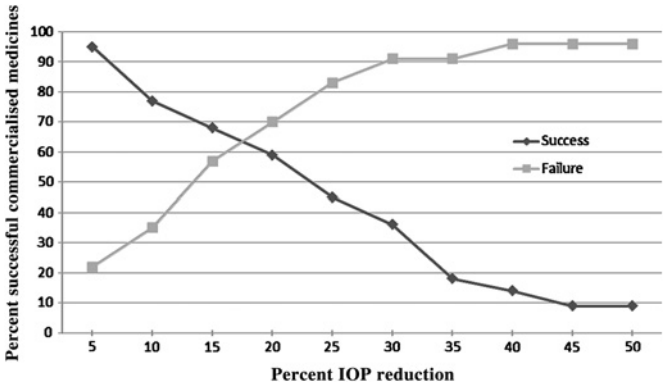

Figure 2 Diurnal pressure reduction for all hypertensive models separated by products that were successfully commercialised or not.

were successfully commercialised (31.5±4.6) and those that were not (32.4±3.3, p=0.44). However, there was no difference in the diurnal or peak pressures between commercialised or non-commercialised medicines in normotensive models.

Figure 2 shows the diurnal pressure reduction for all hypertensive models separated by products that were successfully commercialised or not. Approximately 17.5% reduction identified the maximum number of future commercialised or non-commercialised (~65% each).

Animal model performance: medicine-class-specific

The performance of animal models thought to be useful from the literature evaluating specific commercially available classes of medicines is compared with other assumed non-specific animal models in table 4. No difference was observed for the decrease in pressure between all specific versus non-specific models in commercialised products for either the diurnal or peak pressures, or when comparing specific versus non-specific medicine classes for diurnal and peak pressures in beta-blockers, CAIs or prostaglandins.

DISCUSSION

Animal models are important in the new drug-development process, because they allow for the testing of the efficacy and safety of potential new medicines in a cost-efficient manner that avoids the risk of serious adverse events to humans. Unfortunately, there is no perfect animal treatment model for glaucoma. To increase the specificity of an animal model's ability to indicate commercially viable products, attempts have been made to match the animal and the human physiology based on the class of drug being tested. In general, monkey models have been used to evaluate prostaglandin analogues because this primate's uveoscleral outflow approximates that of the human.[53] In addition, for beta-blockers and topical CAIs, the aqueous dynamics in the monkey and mouse are thought to approximate human physiology more closely.[54] Also, glaucomatous beagles are generally used when evaluating drugs that affect aqueous dynamics.[55]

Further, techniques have been attempted to raise the intraocular pressure elevation in some models to emulate more closely the human disease to allow for a potentially greater reduction in pressure to better differentiate effective from poorly performing medications (tables 1 and 2).

Stewart and coworkers had previously noted that early-phase clinical trial results in Phases I and II were fairly consistent with later-stage Phase III and IV studies for glaucoma medicines.[56] Unfortunately, little prior information has attempted to quantity individual animal model's ability to successfully predict the eventual clinical outcome of the medicine it was used to assess.

The purpose of this analysis was to analyse animal model studies evaluating potential new glaucoma products and determine parameters associated with commercial availability.

Table 4 Individual animal models mean and peak intraocular pressure reduction divided between medications commercially available: percentage mean (percentage range)

		Commercial medications		
Medicine class	**Models**	**Treatment arms**	**Diurnal intraocular pressure reduction**	**Peak intraocular pressure reduction**
Specific*				
Beta-blockers†	Dogs, monkeys	3	34 (27 to 42)	35 (27 to 45)
Carbonic anhydrase inhibitors‡	Monkeys	2	21 (18 to 24)	26 (19 to 33)
Prostaglandins§	Monkeys	9	16 (6 to 26)	20 (8 to 35)
Non-specific*				
Alpha and beta-agonists	Monkeys, rabbits	5	20 (0 to 36)	29 (16 to 52)
Alpha-agonists	Monkeys, rabbits	6	15 (−10 to 75)	30 (−5 to 80)
Beta-antagonists	Rats	2	17 (10 to 24)	19 (12 to 27)
Beta-blockers†	Cats, rabbits	10	15 (−17 to 92)	23 (2 to 92)
Carbonic anhydrase inhibitors‡	Rabbits	1	29	33
Cholinergic agonists	Cats, dogs, monkeys, rabbits	9	19 (0 to 57)	25 (4 to 57)
Prostaglandins§	Dogs, mice, rabbits	7	22 (13 to 39)	30 (19 to 63)

Diurnal/peak p values between:
*Specific and non-specific p=0.67/p=0.63.
†Beta-blockers p=0.31/p=0.45.
‡Carbonic anhydrase inhibitors p=0.37 and p=0.67.
§Prostaglandins p=0.18/p=0.10.

This study found that, as a group, animal models were only partially successful in differentiating medicines that would ultimately become commercially available. Accordingly, much overlap existed in the pressure reduction with medicines that ultimately would become commercially available to those that would not. The percentage reduction in the diurnal decrease in pressure over the first 6 h after instillation that equally differentiated these two groups was 15%. However, this extent of decrease predicted only 55% of the commercialised and non-commercialised medicines.

However, using only hypertensive models improved the differentiation between the commercialised and non-commercialised products available for both the diurnal (p=0.02), but not for the peak (p=0.21) pressure decreases. In contrast, no differences were noted in the percentage pressure decrease in normotensive models for commercialised versus non-commercialised products for the diurnal (p=0.60) and peak (p=0.75) pressures. The reason that the ocular hypertensive models better differentiated more effective medicines in our study probably rests on the fact that a higher baseline intraocular pressure generally allows a greater per cent decrease in treated pressure. Although unproven, this greater reduction in pressure might allow an easier differentiation between treatment groups, at least in humans.[57]

Further, in the four animal types that had direct comparative data between commercially available medicines or those that failed commercialisation, a statistical difference was observed in the diurnal pressure reductions in monkey model studies. However, there was not a greater decrease in diurnal and peak pressures in commercialised medicines in cats, dogs and rabbit studies for diurnal or peak pressure or in monkeys for peak pressure. The reason why the monkey model better differentiated the diurnal pressure between successful and failed medicines is not clear from our results. As noted above, the monkey model typically was used mostly as a hypertensive model and was very commonly employed with the powerful prostaglandin class of medicines. Both of these factors may have allowed for the greater drop in pressure in the monkey animal model.

However, individual models believed to be useful in evaluating specific classes of medicines based on animal physiology thought to be comparable with the human (see above) appeared to provide little benefit over other assumed non-specific models, including: prostaglandins, beta-blockers or CAIs. For these medicines, the pressure reductions were no better for the diurnal or peak pressure decrease with class-specific models than other non-specific models. However, the number of studies was quite small especially for the beta-blockers and the CAIs. Consequently, the results of class-specific model analyses still must be assessed cautiously.

Oddly, the one available fixed combination study provided no greater mean pressure reduction compared with monotherapy. The reason for this is not immediately clear. It may be that the animal models, with or without an induced pressure increase, may not provide a sufficient method to demonstrate the reduction of two medications. Potentially this finding might be specific to the CAI-based fixed combination and other types of fixed combinations might provide a better decrease in pressure. More research to evaluate this question is needed.

This review suggests that animal models provide some success in predicting ultimate commercial launch or failure of a new glaucoma medicine, especially the hypertensive models and the monkey model specifically. However, caution must be used in interpreting individual models or studies.

Further the results of this study generally must be interpreted with caution, and no firm conclusions may be drawn regarding the utility of any individual model generally or for a specific class of medicine. Unfortunately, an insufficient number of studies are available publically that correctly identifies statistically in glaucoma the most accurate animal model to use, either generally or for each specific class of medicine. Further, more studies would better differentiate the level of pressure needed in hypertensive animal models to best differentiate efficacy between products. More exploratory research is needed to evaluate current models and to develop improved techniques that would better predict the commercial usefulness of potential new medicines to better utilise research resources in developing sight-saving new glaucoma medications and limit the risk of exposure to drug-study subjects to ineffective experimental medication.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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