The Japanese Society of Toxicology

Fundamental Toxicological Sciences
URL : http://www.fundtoxicolsci.org/index_e.html

Letter

Risk assessment of reproductive and developmental toxicity in eye-drop drugs: a consideration based on threshold of toxicological concern

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(Received April 10, 2018; Accepted April 16, 2018)

ABSTRACT — The systemic dose levels of eye-drop drugs are relatively low in comparison with that of systemic routes such as oral administration. We undertook overall risk assessment of eye-drop drugs for developmental and reproductive toxicity (DART) by comparing the estimated systemic dose level of eye-drop drugs with the known threshold of toxicological concern (TTC) for DART. The systemic dose level of eye-drop drugs in human were estimated to be 0.0005 to 0.05 mg/kg/day on the assumption of 0.01% to 1% of eye drop formulation, 0.04 mL/eye/time of instillation volume, and 60 kg body weight. The TTCs for DART ranged from 0.003 mg/day (0.00005 mg/kg/day; for anticacer drugs) to 7.860 mg/day (0.131 mg/kg/day). Therefore, the range of estimated systemic dose level of eye-drop drugs was almost overlapped with known TTC values for DART, excepting for that applied to the anticacer drugs. These knowledge simply indicates the safety of eye-drop drugs for DART from a view pont of absolute dosage levels, implying allowance of case by case basis planning non-clinical DART study.

Key words: Eye drop, Risk assessment, TTC, DART

INTRODUCTION

The developmental and reproductive toxicity (DART) of drugs is one of the problematic side effects occurred in systemic administration routes (Briggs *et al*., 2017). Recently, the threshold of toxicological concern (TTC) approach is used for assessing risk of chemicals. This approach is based on the threshold of below which "there would be no appreciable risk to human health" (Kroes *et al*., 2004). Several reports regarding TTC have been issued for DART (Bernauer *et al*., 2008; Laufersweiler *et al*., 2012; Stanard *et al*., 2015; Van Ravenzwaay *et al*., 2011).

Eye-drop drugs are usually applied to human with one or two drops per eye at a frequency of once to several times/day. The systemic exposure level after instilled eye-drop drugs can be imaged to be low as comparison of that of drugs administered systemic routes (*e.g.*, oral route and intravenous injection). However, overall risk of eye-drop drugs against DART has not been investigated.

In this letter article, we undertook to compare the estimated systemic dose level of eye-drop drugs with the reported TTC of DART, in order to comprehensively evaluate the DART risk of eye-drop drugs from a view of its absolute dose level.

MATERIALS AND METHODS

Estimated systemic dose level of eye-drop drugs:

In almost all of cases, the concentration of active pharmaceutical ingredient (API) is 0.01% to 1% in eye-drop drugs (Kurata *et al*., 2016). Therefore, the systemic dose levels of eye-drop drugs in human are estimated to be

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0.0005 to 0.05 mg/kg/day on the assumption of 0.01% to 1% of eye-drop formulation, 0.04 mL/eye/time of instillation volume (Lederer and Harold, 1986), and 60 kg body weight.

The threshold of toxicological concern (TTC):

The TTCs for teratogenicity were quoted from the description by Bernauer *et al.* (2008), Laufersweiler *et al.* (2012), Stanard *et al.* (2015) and Van Ravenzwaay *et al.* (2011). Table 1 summarized the TTC values.

RESULTS AND DISCUSSION

The range of the estimated systemic dose level of eye-drop drugs was almost overlapped with the known TTC values for DART (Fig. 1). The TTC value of Stanard *et al.* (2015), which is set for anticancer drugs, located lower position than the estimated systemic dose level of eye-drop drugs. Since it is well known that the most anticancer drugs such as alkylating agents act directly to genitals and germ cells, it is quite reasonable that the low TTC value is set. It noteworthy that the report by Stanard *et al.* (2015) gave the uncertain factor (namely safety margin) as 100. Whereas, FDA proposed the safety margin for DART as 25 times in the draft guidance (FDA, 2011). By changing the uncertain factor from 100 to 25, the TTC for DART becomes almost close to the estimated systemic dose level of 0.01%. This indicates that the risk of DART in eye-drop drugs is generally low in human clinical usage.

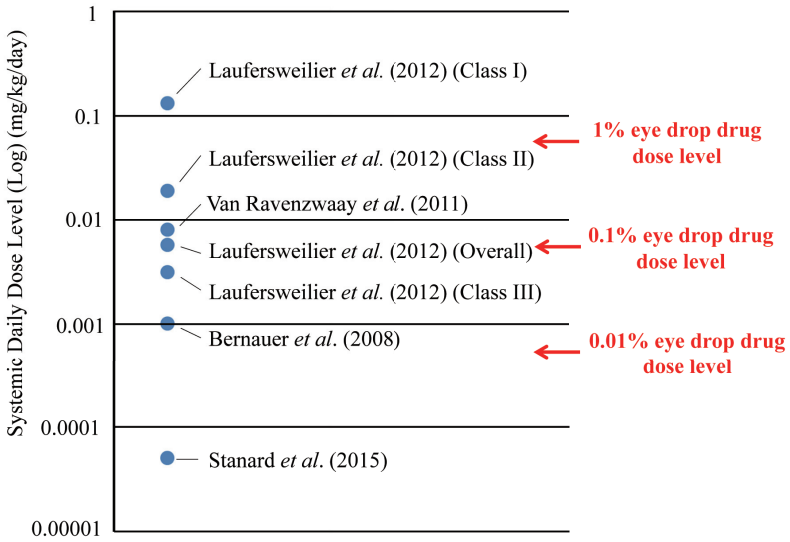

Fig. 1. Comparison between the estimated human systemic dose levels of eye drop drugs and the known TTC levels for developmental/reproductive toxicity. The human systemic dose levels of eye drop drugs are estimated as to be instilled to both eyes with 4 times/day and 0.04 mL/time to 60 kg of human.

Table 1. List of known TTC values for DART.

References	TTC	Note
Stanard *et al.* (2015)	3 μg/day (0.00005 mg/kg)	Developmental toxicity and fertility Anticancer compounds (UF: x100)
Bernauer *et al.* (2008)	60 μg/day (0.001 mg/kg)	Developmental toxicity Chemicals (UF: x1000)
Laufersweiler *et al.* (2012)	186 μg/day (0.0031 mg/kg)	Reproductive toxicity Chemicals (Class III) (UF: x100)
Laufersweiler *et al.* (2012)	342 μg/day (0.0057 mg/kg)	Reproductive toxicity Chemicals (Overall) (UF: x100)
Van Ravenzwaay *et al.* (2011)	480 μg/day (0.008 mg/kg)	Developmental toxicity Chemicals (UF: x500)
Laufersweiler *et al.* (2012)	1122 μg/day (0.0187 mg/kg)	Reproductive toxicity Chemicals (Class II) (UF: x100)
Laufersweiler *et al.* (2012)	7860 μg/day (0.131 mg/kg)	Reproductive toxicity Chemicals (Class I) (UF: x100)

This table was derived from the reference by Stanard *et al.* (2015), and was modified.
The dose per kg body weight was calculated based on human body weight as 60 kg.
UF means uncertain factor.

As shown in Table 1, the TTC values of DART were considerably varied. Stanard *et al.* (2015) described that the TTC of hormone modulators for DART appears to be especially low. The risk of hormone to DART have been well known even in their low dose levels (Briggs *et al*., 2017). Together with expected systemic dose levels of eye-drop drugs, the information of mode of action of its API is of importance in evaluating the risk of DART in eye-drop drugs.

Currently, the TTC approach in evaluating DART is employed in food safety (Magnuson *et al.*, 2013). While, for developing pharmaceuticals, the risk assessment using TTC is employed in assessment of mutagenic impurities for carcinogenic risk currently (ICH, 2014). So far, the TTC approach for risk assessment of DART is not commonly applied in pharmaceutical drugs. This letter implies that the TTC approach would support risk assessment of drugs with very low dose systemic level such as locally applied ones including eye-drop drugs.

The present letter would raise a question in significance of the full set of DART studies. As generally known, safety pharmacology studies may not be needed for locally applied agents (e.g., dermal or ocular) where the pharmacology of the test substance is well characterized, and where systemic exposure or distribution to other organs or tissues is demonstrated to be low (ICH, 2000). In addition, the carcinogenicity study guideline mentions that pharmaceuticals administered by the ocular route may not require carcinogenicity studies unless there is cause for concern or unless there is significant systemic exposure (ICH, 1995). Thinking with the TTC of DART, the limited but "well-designed" DART studies, not full set of DART studies, might be enough in evaluating risk of eye-drop drugs in case by case basis of clinical dose and practical usage in human, and mode of action of API of eye-drop drugs.

In conclusion, this letter suggests overall safety of eye-drop drugs from a view point of their low systemic dose level and generally known TTC of DART, and provides the future discussion regarding the safety assessment and the way of non-clinical DART studies for developing eye-drop drugs.

ACKNOWLEDGEMENT

We are grateful to Drs. Hideyuki Sakaki. of Senju Pharmaceutical Co., Ltd., for advices on the preparation of this manuscript.

Conflict of interest---- The authors declare that there is no conflict of interest.

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