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Use of low-dose clinical pharmacodynamic and pharmacokinetic data to establish an occupational exposure limit for dapagliflozin, a potent inhibitor of the renal sodium glucose co-transporter 2

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ABSTRACT

Classical risk assessment models for setting safe occupational exposure limits (OEL) have used multiple uncertainty factors (UF) applied to a point of departure (POD), e.g., a No Observed Effect Level (NOEL), which in some cases is the pharmacological effect. Dapagliflozin promotes glucosuria by inhibiting the renal sodium–glucose cotransporter-2 transporter. The initial OEL for dapagliflozin (0.002 mg/m^3) was calculated when low dose clinical data was not available to identify a NOEL resulting in the need to use excessive UFs. To reduce the UFs from the OEL, a clinical pharmacodynamic [glucosuria and urinary glucose dipstick (UGD)] and pharmacokinetic study was conducted with single oral doses of 0.001, 0.01, 0.1, 0.3, 1.0 or 2.5 mg administered to 36 healthy subjects. Dose-related dapagliflozin systemic exposures were observed at doses $\geqslant$0.1 mg and glucosuria was observed at doses $\geqslant$0.3 mg and corroborated by UGD. The NOEL was therefore 0.1 mg for glucosuria. For setting the new OEL, no UFs were required. Dividing the POD by 10 m^3 (the volume of air an adult inhales in a workday), the resulting OEL was 0.01 mg/m^3. In conclusion, low-dose clinical pharmacodynamic and pharmacokinetic data can allow the OEL to be adjusted to the highest safe level.

1. Introduction

Occupational exposure limits (OELs) are developed to assist in the control of potential health hazards in the workplace that may result from a worker inhaling substances they are exposed to during the course of their daily activities. OELs are established to protect the worker population from pharmacological as well as toxicological effects. OELs define airborne concentrations of substances with potential biological activity under which it is believed that nearly all workers may be chronically exposed without adverse health effects. They are generally time-weighted average concentrations for a normal 8–10 h workday and a 40-h work week for a 40 year career. OELs are commonplace in the pharmaceutical industry where workers manufacture active pharmaceutical ingredients. Once an OEL is established, validated analytical methods are developed and used to monitor air concentrations of compounds to ensure that the OEL is not exceeded. Medical surveillance of workers is also routinely implemented to verify that the industrial hygiene monitoring is correctly quantifying the potential exposure to the worker.

To develop an OEL, non-clinical toxicological, pharmacological and pharmacokinetic data along with clinical pharmacodynamic, pharmacokinetic and safety data are reviewed. Classical risk assessment models for OELs have used multiple 10-fold uncertainty factors applied to a point of departure (POD), which is the No Observed Effect Level (NOEL) or Lowest Observed Effect Level (LOEL) for the most sensitive endpoint in the most relevant species (EPA, 2002; ICH, 2009). Due to extensive data being available on pharmaceutical ingredients, a data-derived application of uncertainty factors to the POD is used (Sargent and Kirk, 1988; Silverman et al., 1999). Clinical trials are normally designed specifically to understand the safety, tolerability and efficacy at therapeutic doses. Human data describing the effects and pharmacokinetics at sub-therapeutic doses to identify a NOEL upon which an OEL would ideally be based are minimal to non-existent in most cases. The lack of very low dose clinical data relevant to potential workplace exposure levels usually results in the need to use exaggerated uncertainty factors for setting the OEL, even though there is an extensive human dataset on the compound of interest at higher therapeutic doses.

Using the standard approach, an OEL was set for dapagliflozin, a competitive, reversible, and selective renal sodium–glucose

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cotransporter-2 (SGLT2) inhibitor that is being developed as a treatment for type 2 diabetes mellitus (Washburn, 2009; Bailey et al., 2010). A typical robust preclinical and clinical data set was available (Han et al., 2008; Komoroski et al., 2009a,b; List et al., 2009; Bailey et al., 2010; Obermeier et al., 2010). The data show large safety margins between the highest human doses tested without tolerability signals (up to 500 mg) and the therapeutic doses tested in Phase 3 (up to 10 mg). Dapagliflozin blocks the reabsorption of filtered glucose, in turn promoting urinary glucose excretion. Glucose excretion is considered the most sensitive pharmacodynamic effect of exposure to dapagliflozin in rats (Han et al., 2008) and was demonstrated to be a sensitive, dose-dependent marker in humans (Komoroski et al., 2009a,b). The urinary glucose pharmacodynamics of dapagliflozin were evaluated over a dose range of 2.5–500 mg in standard clinical trials, with substantial urinary glucose excretion occurring at all doses studied (Han et al., 2008). Modeling of this data was problematic when extrapolating to lower doses since 2.5 mg was still on the linear phase of the dose–response relationship and the point of departure from linearity at lower doses was therefore unknown. Thus, large uncertainty factors were necessary in setting the original OEL thus resulting in more stringent manufacturing controls being implemented than were actually necessary.

To address the lack of low dose data for dapagliflozin, a clinical pharmacokinetic/pharmacodynamic study was conducted to identify a NOEL for glucosuria and to relieve the uncertainties associated with the dose–response curve developed with the clinically focused data. This paper describes the development of an OEL for dapagliflozin using data from the present study and compares the result to that from the initial OEL setting process. This work shows how conducting a well-designed clinical pharmacology study examining the most sensitive effect of a drug can be used to refine and set a robust OEL. In addition, a complete picture of real life workplace evaluation of air concentrations is presented alongside medical surveillance strategy and results.

2. Materials and methods

2.1. Occupational exposure limit guideline calculations

A standard industry equation modified from Sargent and Kirk (1988) and Silverman and colleagues (1999) using compound-specific factors to calculate OELs is used (Sargent and Kirk, 1988; Silverman et al., 1999).

Equation for calculating the occupational exposure limit:

$$EG = \frac{POD \times ABS}{10\ m^3 \times UF_T \times AF} = \mu g/m^3. \quad (1)$$

where,

- POD = point of departure. This factor represents the LOEL or NOEL in the most relevant study in the most relevant species.
- ABS = absorption fraction. This factor corrects for route of exposure differences (e.g., oral to inhalation).
- 10 m^3 = this factor is the volume of air a 70 kg individual inhales during light to moderate activity in an 8–10 h work day (EPA, 2011).
- UF_T = total uncertainty factor. This factor assesses the uncertainty in the available data set and is discussed below.
- AF = accumulation factor. This factor is used to account for drug accumulation.

The total uncertainty factor (UF_T) evaluates the available data from five aspects: UF_1 NOEL to LOEL, UF_2 interspecies, UF_3 intraspecies, UF_4 subchronic to chronic, and UF_5 miscellaneous factors. Generally, each UF can range from one to ten.

UF_1 *NOEL to LOEL:* A factor of 3 is generally applied if a LOEL was used as the POD. This is based on a comparison of the no observable adverse effect levels (NOAELs) to lowest observed adverse effect levels (LOAELs) from a number of repeat dose studies (Lewis et al., 1990). The average ratio of NOAEL to LOAEL studies from the comparison of subchronic studies was <3; and from chronic studies, the ratio was <3.5 (Lewis et al., 1990). Naumann and Weideman recommend a default of 3-fold (Naumann and Weideman, 1995). Additional information that should be considered when selecting the UF_1 are the steepness of dose–response curve, the severity of effect and the spacing of doses.

UF_2 *interspecies*: Depending on the species used in the study providing the POD, allometric scaling based on body surface area ($W^{0.67}$) is used. For mice, rats, dogs, and monkeys, this corresponds to a factor of 12, 6, 2 and 3, respectively (FDA, 2005). In some cases where the exposure as determined by area under the curve [AUC; or maximum concentration in the blood (C_{max}), as appropriate] is known in both animals and humans, a direct comparison of the AUCs can be conducted to identify the human dose that results in the same exposure-effect in the animal. This derived human exposure-effect dose is used as the POD eliminating the allometric scaling factor. In this case, the species sensitivity to pharmacodynamic effects (e.g., receptor binding) should be examined independently to determine if an additional factor should be applied.

UF_3 *intraspecies*: Commonly, when there is no data, a factor of 10 is used in the risk assessment to account for intraspecies variability (EPA, 2002; ICH, 2009). Renwick and Lazarus have proposed a factor of 10 as a default and that this can be divided into pharmacokinetic (PK) and pharmacodynamic (PD) variability factors using 3.2 for each parameter (Renwick and Lazarus, 1998). However, if PK or PD data are available the factor can be refined as follows. The variability around the clinical pharmacokinetic exposure results at steady state, either AUC or C_{max} depending on the exposure relationship to the POD effect, is examined. The ratio of the upper confidence limit of the AUC (or C_{max}) to the mean AUC (or C_{max}) is used in place of the default 3.2 factor for PK. In some cases, the lowest PD effect at the POD is known and understood. In this case, the variability of the measured effect value is used to calculate a ratio of the upper confidence limit to the mean effect value. The PD ratio then replaces the PD default factor of 3.2.

UF_4 *subchronic to chronic*: This factor addresses the potential for a decreased NOEL being identified when the length of a study is extended from a subchronic to a chronic duration. McNamara and colleagues (1976) examined 74 data sets of which 85% of the compounds had a ratio of 3.3 or less when dividing the NOEL value in a subchronic study (30–90 days) to that in a chronic study (2 years) (McNamara, 1976). In an additional 18 data sets examined by Lewis and colleagues, the ratio was 1.6–2.5 when subchronic NOEL values were divided by chronic NOEL values (Beck et al., 1993). Thus, a factor of 3 is applied if chronic data are not available.

UF_5 *miscellaneous factor*: The miscellaneous factor allows for professional judgment and ranges from 1 to 10 when there are concerns about lack of data, quality of the data, severity of effects, route of exposure, or other unaccounted for uncertainties in the data.

Preclinical and clinical pharmacological, pharmacokinetic, toxicological and safety data on dapagliflozin used for determining the original OEL are summarized in previous publications (Han et al., 2008; Komoroski et al., 2009a,b; List et al., 2009; Bailey et al., 2010; Obermeier et al., 2010).

2.2. Low dose clinical pharmacokinetic/pharmacodynamic study in healthy subjects

The study protocol for determining the low dose (0.001–2.5 mg) pharmacokinetics and pharmacodynamics of dapagliflozin in healthy subjects was approved by the local institutional review