Mathematical model formulation

The F amount rate in plasma (dF/dt) depends on the contribution of: F by bone (kr*[F]b), F incorporation to bone tissue (kf*[F]p), urinary excretion (ku*[F]p), chronic food and water ingestion (I) and F absorption by an oral dose (kg*D), as it is depicted in Equation 1

$$\frac{dF}{dt} = kr*[F]_b - kf*[F]_p - ku*[F]_p + I + kg*D$$

Equation 1

In the absence of an oral dose of F, the variation of plasma F concentration can be written as shown in Equation 2, which equals zero, since the [F]p variation remains constant.

$$\frac{dF}{dt} = 0 = kr*[F]_b - kf*[F]_p - ku*[F]_p + I$$

Equation 2

As it was demonstrated in the previous work kr*[F]b = BR y kf*[F]p = BF .
The term ku*[F] p will be called Ub, which represents the basal rate of fluoride excretion in urine that is calculated as the amount of fluoride excreted divided by the period of time considered. Therefore, Equation 2 might be write as:

$$0 = BR - BF - Ub + I$$

Equation 3
rewriting

$$BR - BF = Ub - I$$

Equation 4
After an oral dose of F, kr*[F]b might be consider negligible with respect to kf*[F]p since [F]p (plasma F concentration) is much higher than [F]b. Also, if the F dose is higher than the daily ingestion of F (I), I parameter will be consider negligible with respect to kg*D. Therefore, Equation 1 might be written as:

$$\frac{dF}{dt} = -kf*[F]_p - ku*[F]_p + kg*D$$

Equation 5

Operating and calling:
ke = kf + ku
the next Equation 6 is obtained:

$$\frac{dF}{dt} = -ke * [F]_p + kg * D$$

Equation 6

Fluoride concentration might be express as: [F] = F /Dv, where F is the amount of fluoride in a distribution volume, Dv, the next equation is obtained:

$$\frac{dF}{dt} = -ke * \frac{F}{Dv} + kg * D$$

Equation 7

Applying Laplace transform to solve Equation 7:

$$s * \overline{F} - F_o = \frac{-ke}{Dv} * \overline{F} + kg * \overline{D}$$

Equation 8

Fluoride absorption in the digestive tract follows a mono-exponential decline function, as has been shown in other studies, this is depicted in the next Equation 9:

$$\frac{dD}{dt} = -kg * D$$

Equation 9

Applying Laplace transform:

$$s * \overline{D} - D_o = -kg * \overline{D}$$

Equation 10

$$\overline{D} = \frac{D_o}{(s + kg)}$$

Equation 11

Substituting Equation 11 in Equation 8 and solving the resulting Laplace inverse transform we reach to the Equation 12. Both terms of the equation were divided by Dv, so that the final Equation 12 would be expressed in terms of concentration and not amount of F.

$$[F] = \frac{kg * Do}{\left(\frac{ke}{Dv} - kg\right) * Dv} * \left(e^{-kg * t} - e^{\left(\frac{-ke}{Dv} * t\right)}\right)$$

Equation 12

We consider that [F]p,o is the basal plasma F concentration, so we add this constant to Equation 12, obtaining:

$$[F]=\frac{kg*Do}{(\frac{ke}{Dv}-kg)*Dv}*(e^{-kg*t}-e^{(\frac{-ke}{Dv}*t)})+[F]_{p,o}$$

Equation 13

Equation 13 is the function that models plasma F concentration after an oral dose of F. Taking into account urinary F excretion, regarding that F filters freely at glomerular level, urinary excretion is proportional to plasma F concentration.

$$\frac{dU}{dt}=ku*[F]_p$$

Equation 14

Urinary F excretion is written replacing in Equation 14, the Equation 13:

$$\frac{dU}{dt}=\frac{ku*kg*Do}{(\frac{ke}{Dv}-kg)*Dv}*(e^{-kg*t}-e^{(\frac{-ke}{Dv}*t)})+ku*[F]_{p,o}$$

Equation 15

Integrating Equation 15 as a function of time, the next equation is obtained:

$$U=\frac{-ku*Do}{(\frac{ke}{Dv}-kg)*Dv}*(e^{-kg*t}-1)+\frac{ku*kg*Do}{(\frac{ke}{Dv}-kg)*ke}*(e^{\frac{-ke}{Dv}*t}-1)+ku*[F]_{p,o}*t$$

Equation 16

The first two terms of Equation 16 16 are the urinary F excretion after a dose and the urinary basal F excretion, respectively. The former is obtained from the daily F ingestion (I) and bone resorption.

Reordering Equation 16, we obtained:

$$U-ku*[F]_{p,o}*t=\frac{-ku*Do}{(\frac{ke}{Dv}-kg)*Dv}*(e^{-kg*t}-1)+\frac{ku*kg*Do}{(\frac{ke}{Dv}-kg)*ke}*(e^{\frac{-ke}{Dv}*t}-1)$$

Equation 17

The first term in Equation 17 represents the difference between urinary F excretion after an oral dose of F and urinary F excretion without a F dose, we will named this difference: ΔU.

$$\Delta U=\frac{-ku*Do}{(\frac{ke}{Dv}-kg)*Dv}*(e^{-kg*t}-1)+\frac{ku*kg*Do}{(\frac{ke}{Dv}-kg)*ke}*(e^{\frac{-ke}{Dv}*t}-1)$$

Equation 18

After 24 h the exponential terms have a value near to -1, therefore Equation 18 might be write as:

$$\Delta U = \frac{-ku * Do}{(\frac{ke}{Dv} - kg) * Dv} * (-1) + \frac{ku * kg * Do}{(\frac{ke}{Dv} - kg) * ke} * (-1)$$

Equation 19
or

$$\Delta U = \frac{ku * Do}{(\frac{ke}{Dv} - kg) * Dv} - \frac{ku * kg * Do}{(\frac{ke}{Dv} - kg) * ke}$$

Equation 20
Reordering:

$$\Delta U = \frac{ku * Do * ke - ku * kg * Do * Dv}{(\frac{ke}{Dv} - kg) * Dv * ke}$$

Equation 21
And operating:

$$\Delta U = ku * Do \frac{(ke - kg * Dv)}{(ke - kg * Dv) * ke}$$

Equation 22
This results in Equation 23:

$$\Delta U = \frac{ku * Do}{ke}$$

Equation 23
From equation 23 the value of ke might be obtained:

$$ke = \frac{ku * Do}{\Delta U}$$

Equation 24
As it was explained before:

$$ke = kf + ku$$

Equation 25
Reordering:

$$kf = ke - ku$$

Equation 26
And the value of kf might be obtained:

$$kf = \frac{ku * Do}{\Delta U} - ku$$

Equation 27

$$kf = ku * \left(\frac{Do}{\Delta U} - 1\right)$$

Equation 28

As it was stated before Ub = ku[F]p, therefore reordering we reached to:
ku= Ub/[F]p
In absence of F dose, Ub is constant and might be calculated as the division between the urinary F excretion in absence of F dose (Uo) and the time interval (t). As it is shown next:
Ub = Uo / t
ku= Uo/[F]p*t
Taking these equations into account, the next equation is obtained:

$$kf = \frac{Uo}{[F]_p t} * \left(\frac{Do}{\Delta U} - 1\right)$$

Equation 29

As BF = kf – [F]p:

$$BF = kf * [F]_p = \frac{Uo}{[F]_p t} * \left(\frac{Do}{\Delta U} - 1\right) * [F]_p$$

Equation 30

Reordering:

$$BF = \frac{Uo}{t} * \left(\frac{Do}{\Delta U} - 1\right)$$

Equation 31

Subtracting BF in Equation 4, the next equation is obtained:

$$BR = \frac{Uo}{t} * \left(\frac{Do}{\Delta U} - 1\right) - \frac{Uo}{t} - I$$

Equation 32

Reordering:

$$BR = \frac{Uo}{t} * \frac{Do}{\Delta U} - \frac{Uo}{t} - \frac{Uo}{t} - I$$

Equation 33

This results in:

$$BR = \frac{Uo}{t} * \frac{Do}{\Delta U} - I$$

Equation 34