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MSc in Forensic Medical Sciences

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The use of a hydraulic model to demonstrate the relationship between apparent volume of distribution, clearance, and elimination rate constant

Introduction

The elimination of drugs has always been an important subject matter in toxicology. It is important to understand the rate of elimination for drugs currently available on the market due to increase in drug of abuse. The aim of this report is to provide a simple overview of how drug concentration are obtained, compared, and eliminated using a hydraulic model (Buclin *et al*., 2009).

In police investigation, the detection of drugs may play a vital role in the prosecution and defence. Within the UK, drugs are commonly involved in violence, public disorders and drug facilitated sexual crime. The time course for drug metabolism involves liberation, absorption, distribution, metabolism and elimination. However not all drugs are metabolised by the liver, some may stay in its original form. The rate of elimination is totally dependent on the type of drug and the user's tolerance. It is normally possible to back track the time of consumption and initial dose by performing different toxicology experiment. The significant part of Toxicology is comparing the known to the unknown, standard solutions are used to calibrate laboratory equipment in order to obtain a viable reading. The standard solution normally contain the drug itself or its metabolites, depending on the substances screening for (Bourne, 2010).

The hydraulic model created within this experiment can reveal the mechanism of drug elimination in a simple form but provide realistic data for analysis purposes. The hydraulic model mimic the human body excretion organs e.g. lung, kidney and liver, which eliminate drugs from our system. The theoretical drug used in this experiment, sodium salicylate, will be tested to demonstrate how the reading of drug concentration can be obtained, with further mathematical calculations the half-life, volume of distribution, rate of elimination can also be calculated (Bourne, 2010 and Buclin *et al*., 2009).

Method

Apparatus & reagent

- Buchner flasks
- Cuvettes
- Fluorometer
- Magnetic stirrer
- Pipettes
- Sodium Salicylate solution, 50mg/mL
- Stop Clock
- Variable flow taps

Initially the Buchner flask was placed on top of a magnetic stirrer with the entry side arm connected to a variable flow tap via a rubber tube. The flow of water was adjusted to 10ml/min and the exit side arm should be placed in a fashion where the water can flow freely. The magnetic stirrer was switched on and 1 mL of sodium salicylate solution was added. The clock was started immediately. 1 mL of samples were drawn out 0.5, 1, 2, 5, 10, 20, 30 min and transferred to the cuvettes using a pipette. 0.5mL of samples were further transferred to a separate cuvette. 2.5mL of distilled water were added to each of the samples and their fluorescence were measured using a fluorometer at 420nm.

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Second part of the experiment involved a serial dilution of the sodium salicylates solution 50mg/mL. 6 different concentrations of salicylate solution 12.5, 25, 50, 100, 200, 400 mg/L were created in a cuvettes. 2.5mL of distilled water were added to 0.5ml of each samples. The fluorescence of the samples were measure using a fluorimeter at 420nm.

The flow rate of the tap was determined by measuring the time taken to fill a beaker with 100ml of water. The experiment was later repeated by varying the flow rate of the tap to 35ml/min.

Results

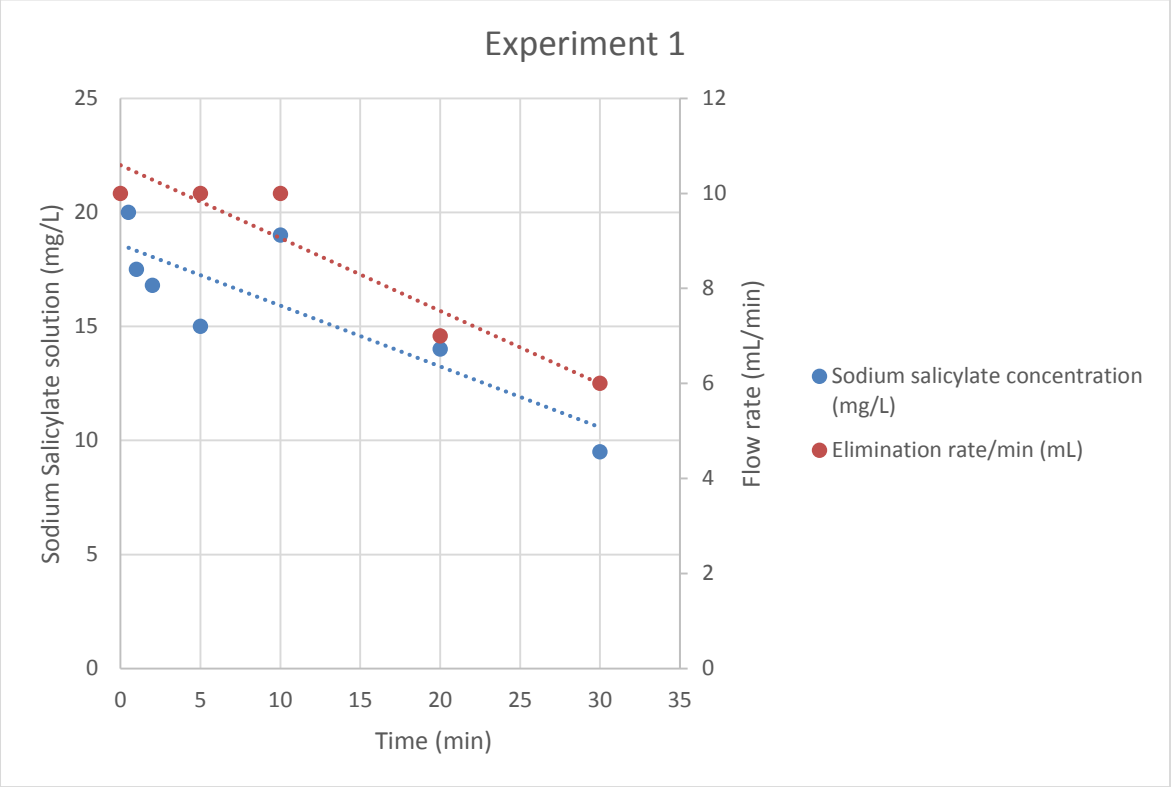

Figure 1 –The flow rate for experiment 1 was set at 10ml/min. However the flow rate did fluctuate during the experiment. The absorbance of the samples were also recorded which was translated to drug concentration, it is showing a rough linear decrease as the time increases.

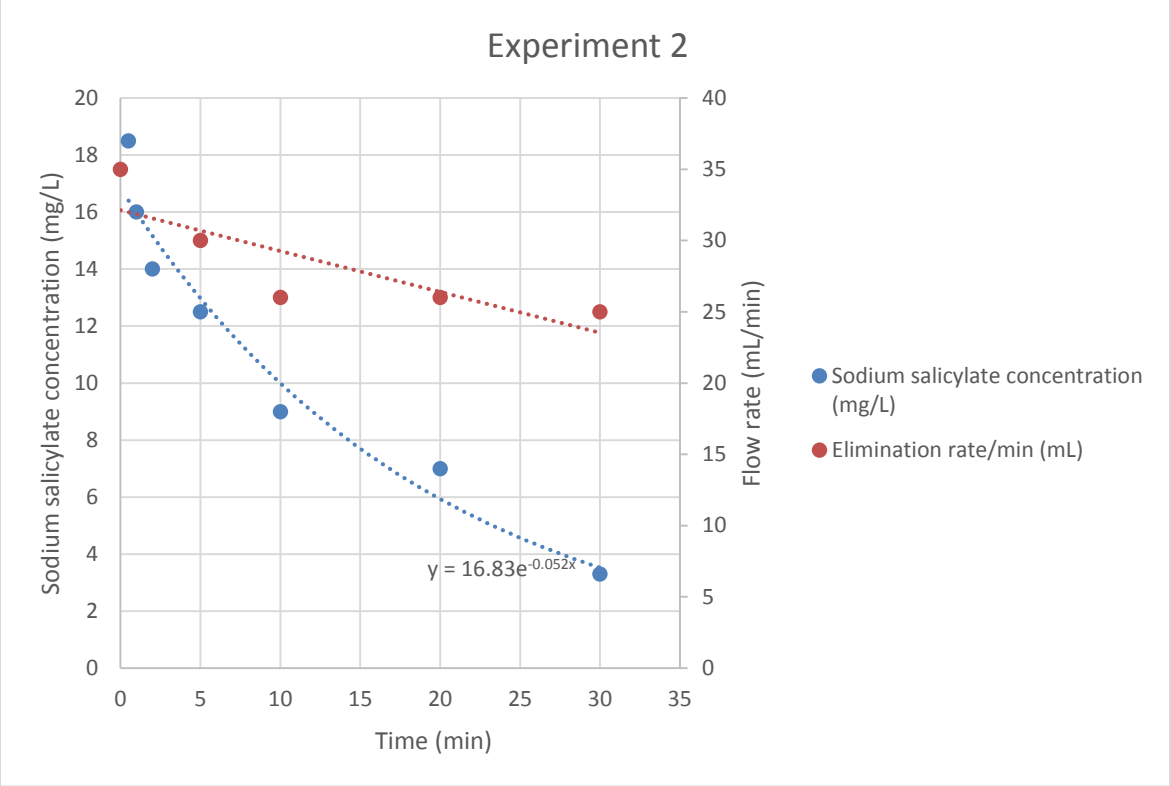

Figure 2 – Experiment 2 is a repetition of experiment 1, it uses the same procedure to obtain absorbance reading from the samples. However the flow rate have been adjusted to 35mL/min. The absorbance of samples is showing a relatively steep decline as the time increases.

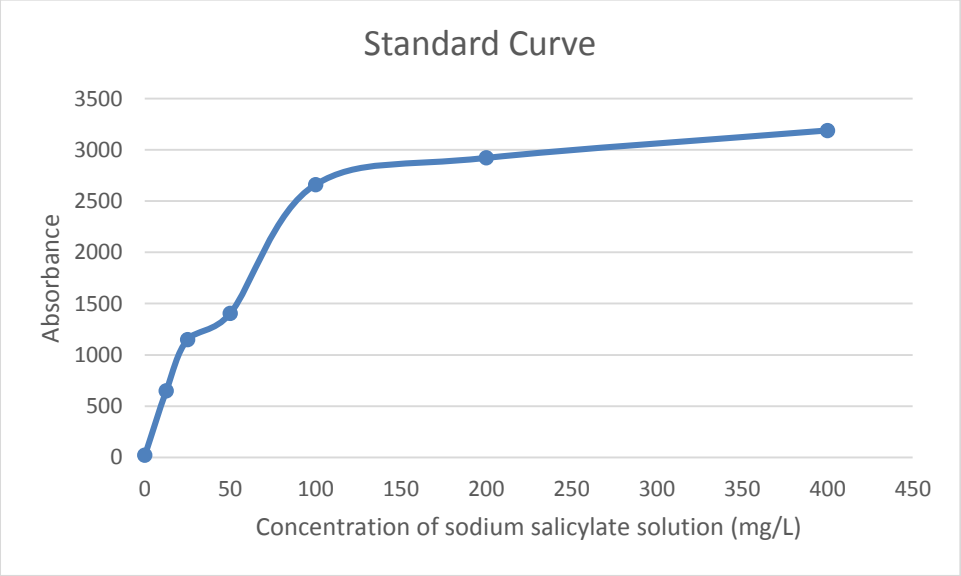

Figure 3 – A Standard absorbance curve generated using the samples obtained from the second part of the experiment. It is showing an increase in absorbance as the concentration of sodium salicylate increases.

Volume of distribution=50mg/18.5mg/L

Volume of distribution=2.7L

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Clearance=2.7L*52mg/mL/min

Clearance=140.4ml/min

Half-life=0.693/ 0.052mg/L/min

Half-life=13.32 min

Discussion

It is very important to understand the direct relationship between drug elimination and clearance. In theory the rate of elimination and plasma drug concentration dictate the rate of clearance, which means to obtain a faster clearance a higher rate of elimination and lower drug plasma concentration is ideal (Buclin *et al*., 2009).

Figure 1 and 2 contains water flow rate data, which was recorded during the experiment. According to both figures, it seems the slight variation of water flow rate did not have a significant impact on the experiments. Due to the outlier in figure 1 it is impossible to tell the impact of flow rate variance on the experiment. However the data from figure 2 did show at the initial 5 minute the concentration of drug within the solution have decreased from 18.5ml/L to 10.5L at the flow rate of 35ml/min to 30ml/min. As the flow rate decreases it seems the rate of elimination have also decreased by 2ml per every 10 minute, but the data is inconclusive. It is common that the drug elimination slows down at each successful half-life.

The drug concentration reading used in figure 1 and 2 were directly translated using the standard curve from Figure 3. It was generate by measuring the absorbance of the serial diluted sodium salicylate solutions. However, the data collected from experiment 1 is showing degree of unreliability. It seems an errors has been made at 10 minute mark. It could possibly due to equipment error. Therefore considering the possibility of underlying errors, data from experiment two were chosen for pharmacology calculations.

The volume of distribution also known as apparent volume of distribution is often used to calculate the dosage of drugs required for medical treatment. The data from experiment 2 have given a 2.7 litre of plasma for volume of distribution. Realistically, it is a relatively low plasma concentration with regards to the administered dose. Drugs with very small Volume of distribution may occur because the molecule is too large or binds to a plasma proteins reducing its availability in organs and other tissue molecules. However the drug concentration at zero time is less than half of the initial dose, it should not occur in this experiment. (lynn, 2007).

The rate of drug clearance is 140.4ml/min meaning every min 140.4ml of plasma fluid is completely cleared of drug. This is often the function of elimination organs within our body, within this hydraulic model there are no elimination organs, drugs can flow freely without the interruption of biological factors e.g. enzyme (Bourne, 2010). The half-life for sodium salicylate solution used in this specific hydraulic model is 13.32 min. At 13.32 min the amount of drug left within the system have decreased to half of its original dose, which is roughly 9mg/L. Each successful half-life normally results in less drug elimination in the next, which is shown in figure 1 and 2. A rapid decline of sodium salicylate solutions occured at the first 5 -10 mins of the experiment. The rate of elimination slow down after roughly half life was reached (Buclin *et al*., 2009).

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This hydraulic model can only demonstrate the simplest form drug ingestion and elimination. The effect of equipment errors must not be overlooked. The pipette used in the experiment carry a 1.15% error rate, meaning every 1ml of liquid drawn it could contain +/-0.015ml. The fluorescence spectrometer Hitachi F2000maxi fluoresce do have some possible faults as stated in the user manual, the equipment is unable to detect low or high concentration of drugs, at high concentration the detection beam is unable to focus at the centre of the sample resulting in false reading (Hitachi high technology cooperation, 2001). Also the design of the Buchner flasks contain a big flaw. The exit side arm is located at the middle of the flask rather than the bottom, meaning majority of the drugs are lost before it can reaches the bottom of the flasks, which could be the reason of rapid drug losses at the initial stage, leading to a low volume of distribution.

Conclusion

To conclude, this experiment has demonstrated the realistic side of drug elimination in a human body. The low volume of distribution have suggested large volume of drug were lost prior to the start. This is already an indication of possible equipment fault. The Florence spectrometer is a relatively old model and it contain a degree of flaws within its design, which could have an impact on the absorbance reading. Another major problem experienced is the uncontrollable flow rate of water. Considering all of the problems above the results obtained should be evaluated with caution. The hydraulic model should be considered as the simplest form of system representing drug elimination of the human body

Referencing

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