HEAT TRANSFER IN PATIENTS UNDER HYPOTHERMIC CONDITIONS

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ABSTRACT. Most bio-heat transfer models for patients under hypothermic conditions contain three sub-models: a passive heat transfer model, an active coupling between local blood flow and temperature, and a pharmacological model to incorporate the effects of drugs. In this paper an illustrative example will be given focussed on scalp cooling to prevent chemotherapy induced hair loss. Scalp cooling can reduce hair loss. Unfortunately, the efficacy of scalp cooling varies strongly. A systematic evaluation of the current hypothesis for the hair preservative effect of scalp cooling is necessary for a better understanding of the various important parameters of scalp cooling. To quantify the contribution of the putative mechanisms of scalp cooling, a computational model was developed, partly based on experimental data. With the complete model, we evaluated the effect of several scalp cooling protocol parameters.

Keywords: Bio-heat transfer, Scalp cooling, Pharmacokinetic model

INTRODUCTION

Chemotherapy induced hair loss is a feared side effect of cancer treatment [1]. Scalp cooling during the administration of cytotoxic drugs can reduce this hair loss [2]. Cooling can be achieved by means of a cap, that is pre–cooled in a freezer or that exchanges coolant with a reservoir. The current hypothesis for the hair preservative effect of scalp cooling is that cooling of the scalp skin reduces blood flow (perfusion) and chemical reaction rates [3]. Reduced perfusion leads to less cytotoxic drugs available for uptake, while the reduced temperature decreases uptake of and damage by chemotherapy. Altogether, less damage is done to the hair cells, and the hair is preserved.

To support this hypothesis, we conducted a series of in vitro biological cell experiments in an earlier study [4], in which local tissue concentrations were related to cell damage at different temperatures. A typical result is given in figure 1. Cell survival significantly increased with decreasing doxorubicin concentrations. When compared to an exposure temperature of 37°C, a decrease in temperature also has a significant increasing effect on cell survival. No significant differences were found between exposure temperatures of 22°C and 10°C. At a concentration of 0.5 µg ml⁻¹, cell survival increased from 41% (37°C) to 85% and 89% by reducing temperature to 22°C and 10°C, respectively.

However, the effect of scalp cooling in clinical practice varies strongly [5]. A systematic evaluation of the current hypothesis is necessary for a better understanding of the various important parameters of scalp cooling.

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In the present study, we want to quantify the contribution of the putative mechanisms by which scalp cooling prevents hair loss. To that end, a computational model has been developed based on the current hypothesis of the mechanisms of scalp cooling. The full computational model consists of sub-models that describe heat transfer in the human head, perfusion through the scalp skin as function of temperature and transport of doxorubicin (a specific chemotherapy agent) in the human body. Experiments have validated and improved the different computational models. As the heat transfer model and the skin perfusion relation is already published elsewhere [6, 7], we will here mainly focus on the pharmacokinetic model.

**METHODS**

**Heat transfer model**

Although more complicated models can be used to analyze heat transfer in perfused tissues [8], in this study a one dimensional heat transfer model was used, that uses the Pennes’ equation to describe heat transfer in the human head during scalp cooling. The model consists of several tissue layers, representing the brain, skull, fat, skin, hair and cold cap. Model properties are shown in table 1, in which $q_m$ represents the metabolic heat production and $w_b$ the perfusion. For a more detailed description of the heat transfer model of the head, the reader is referred to [6]. Parameter studies with the heat transfer model showed that key parameters that determine the actual skin temperature during scalp cooling are the size of both the sub–cutaneous fat–layer and the hair–layer.
Table 1
Thermophysical Tissue Parameters used in the Heat Transfer Model (from [6])

<table>
<thead>
<tr>
<th></th>
<th>d</th>
<th>k</th>
<th>c</th>
<th>(\rho)</th>
<th>(q_m)</th>
<th>(w_b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>88.0</td>
<td>0.5</td>
<td>3800</td>
<td>1000</td>
<td>8800</td>
<td>8.5</td>
</tr>
<tr>
<td>Skull</td>
<td>5.4</td>
<td>1.0</td>
<td>1700</td>
<td>1500</td>
<td>130</td>
<td>0.150</td>
</tr>
<tr>
<td>Fat</td>
<td>3.0</td>
<td>0.2</td>
<td>2390</td>
<td>1050</td>
<td>130</td>
<td>0.2</td>
</tr>
<tr>
<td>Inner skin</td>
<td>1.0</td>
<td>0.384</td>
<td>3570</td>
<td>1130</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Outer skin</td>
<td>1.0</td>
<td>0.384</td>
<td>3570</td>
<td>1130</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hair</td>
<td>2.5</td>
<td>0.04</td>
<td>1000</td>
<td>1</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cold Cap</td>
<td>10.0</td>
<td>0.500</td>
<td>4300</td>
<td>1000</td>
<td>0</td>
<td>119.0</td>
</tr>
</tbody>
</table>

Relationship between temperature and blood flow
As an input in the heat transfer and pharmacokinetic models a relation is needed between local skin temperature and local skin perfusion. In an earlier study [7], we established such a relationship using laser Doppler flowmetry and thermocouple measurements and the result is given in figure 3.

Relative perfusion as a function of the temperature difference appeared to be well described by:

\[
\Phi_{wr} = \frac{w_b}{w_{b,0}} = \Phi_{min} + (1-\Phi_{min})e^{\frac{T-T_0}{\Theta}}
\]

in which \(w_{b,0}\) and \(T_0\) are the perfusion and temperature in neutral state. The limit in perfusion, \(\Phi_{min}\), was found to be equal to 18%, and the rate of change, \(\Theta\), was found to be equal to 4.3ºC, indicating that 95% of the drop in perfusion is reached for a temperature difference of approximately 13ºC.

Pharmacokinetic model
An eight–compartment physiologically based pharmacokinetic (PBPK-) model for doxorubicin was developed. It is largely based on a previous model for doxorubicin [9], with some modifications. A schematic of this model is shown in figure 4.
The standard model represents a female with a body mass of 70 kg and a body height of 1.67 m, which is in agreement with the mean of the Dutch female population in 2002. For each compartment, a generic tissue mass balance for doxorubicin is formulated:

$$\frac{dA_T}{dt} = W_B (C_A - C_V) - M$$

(2)

in which $A_T$ (mol) is the amount of doxorubicin in the tissue, $W_B$ (m$^3$ s$^{-1}$) is the volumetric blood flow rate through the tissue, $C_A$ and $C_V$ (mol m$^{-3}$) are the arterial concentration entering the tissue and the venous concentration leaving the tissue, respectively, and $M$ (mol s$^{-1}$) is the rate of metabolism and/or excretion of doxorubicin in the tissue. Values for blood flow and tissue volume used in the standard model are shown in table 2.

Table 2

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$W_B$ (1/min)</th>
<th>$V_T$ (l)</th>
<th>$T_{DNA}$ (μM)</th>
<th>$T_{CAL}$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.35 ± 0.05</td>
<td>1.82 ± 0.28</td>
<td>23.7 ± 2.3</td>
<td>44.6</td>
</tr>
<tr>
<td>Heart</td>
<td>0.26 ± 0.04</td>
<td>0.35 ± 0.04</td>
<td>8.3 ± 4.0</td>
<td>43.8</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.05 ± 0.08</td>
<td>0.28 ± 0.03</td>
<td>16.2 ± 2.2</td>
<td>52.3</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>0.29 ± 0.02</td>
<td>1.47 ± 0.14</td>
<td>19.1 ± 13.7</td>
<td>25</td>
</tr>
<tr>
<td>Gut</td>
<td>1.17 ± 0.11</td>
<td>1.19 ± 0.13</td>
<td>25.2 ± 2.3</td>
<td>25</td>
</tr>
<tr>
<td>Slowly Perfused</td>
<td>1.57 ± 0.15</td>
<td>51.2 ± 5</td>
<td>4.5</td>
<td>15</td>
</tr>
<tr>
<td>Scalp Skin</td>
<td>0.29 ± 0.03</td>
<td>2.89 ± 0.28</td>
<td>4.5</td>
<td>5</td>
</tr>
<tr>
<td>Blood</td>
<td>5.84</td>
<td>5.53</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values for perfusion and volume are obtained from [10], values for binding capacity are taken from [9]. Values are shown as mean ± standard deviation.

To account for saturable chemical-specific binding, a partitioning coefficient $K_p$ was introduced [9], which relates the venous concentration to the tissue concentration:

$$C_V = \frac{1}{K_p} C_T$$

(3)
Here the partitioning coefficient is mathematically represented by [11]:

\[
K_p = \left(1 + \frac{T_{DNA}}{K_{DNA} + C_T} + \frac{T_{CAL}}{K_{CAL} + C_T}\right)
\]  

(4)

with \(T_{DNA}\) and \(T_{CAL}\) the DNA and cardiolipin binding capacity available and \(K_{DNA}\) and \(K_{CAL}\) the binding affinities of doxorubicin to DNA and cardiolipin, respectively (see table 2), and \(C_T\) the doxorubicin tissue concentration \(C_T = A_T/V_T\). The affinity constants for DNA and cardiolipin are set to \(K_{DNA} = 200\) nM and \(K_{DNA} = 400\) nM, respectively (see table 3).

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Standard model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass [1]</td>
<td>(m_b)</td>
<td>70 kg</td>
</tr>
<tr>
<td>Height [1]</td>
<td>(h_b)</td>
<td>1.69 ± 0.2 m</td>
</tr>
<tr>
<td>BMI [1]</td>
<td>-</td>
<td>24.5 ± 1.7 kg m(^{-2})</td>
</tr>
<tr>
<td>Surface Area</td>
<td>-</td>
<td>1.8 m(^2)</td>
</tr>
<tr>
<td>Cardiac Output [2]</td>
<td>(W_{CO})</td>
<td>5.81 min(^{-1})</td>
</tr>
<tr>
<td>Dox fraction bound to blood [3]</td>
<td>(F_B)</td>
<td>0.7</td>
</tr>
<tr>
<td>Affinity constant for DNA [3]</td>
<td>(K_{DNA})</td>
<td>200 nM</td>
</tr>
<tr>
<td>Affinity constant for cardiolipin [3]</td>
<td>(K_{CAL})</td>
<td>400 nM</td>
</tr>
<tr>
<td>Fraction renal blood flow cleared [3]</td>
<td>(F_f)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

[1] Based on data obtained from Statistics Netherlands (CBS)

Binding to proteins in the blood is also accounted for. It is assumed that only unbound drug concentration in the blood \(C_A\) is available for uptake in the tissue – except for the liver, where total drugs \(C_{BL}\) is available for uptake. The fraction of doxorubicin that is bound to plasma proteins is equal to \(F_B = 0.7\) [9]. The blood compartment mass balance may now be specified as:

\[
\frac{dA_B}{dt} = \sum_i W_{B,i} C_{BL,i} - C_A W_{CO} - W_{B,LE} (C_{BL} - C_A)
\]

(5)

where \(W_{CO} = \sum W_{B,i}\) is the total cardiac output. With \(A_B\) (mol) the amount of doxorubicin in the blood, the total arterial concentration \(C_{BL}\) and unbound arterial concentration \(C_A\) are defined as:

\[
C_{BL} = \frac{A_B}{V_B}
\]

\[
C_A = C_{BL} (1 - F_B)
\]

(6)

In some tissues doxorubicin is metabolized to non–harmful products. In the liver, kidney and the heart, doxorubicin is metabolized to doxorubicin aglycone (AG), which can be described by a linear process:

\[
M_{AG} = K_{AG} C_T V_T
\]

(7)
Other metabolic processes include the metabolism by aldo–keto reductase (AKR) to doxorubicinol in the liver and the kidney, and excretion in the faeces by P–glycoprotein (PGP) in the liver and the gut. Michaelis–Menten kinetics may be used to describe these processes:

\[
M_{\text{AKR, PGP}} = \frac{v_{\text{max, AKR, PGP}} C_T}{K_m - \text{AKR, PGP} + C_T}
\]

Finally, excretion of doxorubicin by filtration in the urine in the kidney compartment is modelled by:

\[
M_f = F_x \cdot W_B \cdot C_A
\]

Values for metabolic activity that are used in the pharmacokinetic model under standard conditions are shown in table 4. For each tissue compartment, see equations 2 and 5, a single ordinary differential equation (ODE) is obtained. The complete set of ODEs is solved using MATLAB.

<table>
<thead>
<tr>
<th></th>
<th>AG\textsuperscript{[1]}</th>
<th>AKR\textsuperscript{[2]}</th>
<th>PGP\textsuperscript{[2]}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(K_m)</td>
<td>(V_m)</td>
<td>(K_m)</td>
</tr>
<tr>
<td>Liver</td>
<td>12104</td>
<td>275</td>
<td>1804</td>
</tr>
<tr>
<td>Kidney</td>
<td>484</td>
<td>539</td>
<td>3161</td>
</tr>
<tr>
<td>Heart</td>
<td>760</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gut</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{[1]} The first order rate constant \(K_m\) for metabolism to aglycone (AG) is expressed in (h\(^{-1}\) kg tissue\(^{-1}\)).

\textsuperscript{[2]} The activities for aldo–keto reductase (AKR) and P–glycoprotein (PGP) are expressed as \(K_m\) (\(\mu\)M) and \(V_m\) (\(\mu\)mol h\(^{-1}\) kg tissue\(^{-1}\)).

**RESULTS**

**Validation**

Unfortunately, there is hardly any data available describing the doxorubicin concentration in time for individual organs in humans. Currently, only blood serum levels in time are available in literature. This means that the results of the model can only be compared to these blood serum levels, and that the model cannot be validated on the scale of individual organs. However, the concentration in the blood serum is a direct result of the distribution, metabolism and excretion of doxorubicin in individual organs. When the model accurately predicts blood serum levels, it is very likely that the concentration levels in each individual organ are of the correct order. Therefore, we compared blood serum levels from the study of Andersen \textsuperscript{[12]} with results from our model. Figure 5 shows the blood plasma concentration (mean ± SD) of 24 patients receiving a dose of 50 mg m\(^{-2}\) as a 10 minute infusion. The results of our model describe the measured data well; peak concentration, first half–life time and final half–life time are predicted within the range of intra–individual variation.
Figure 5: Blood plasma concentrations obtained by the pharmacokinetic model (–) compared to the average blood plasma concentration (○, mean ± SD) of 24 patients receiving a dose of 50 mg m$^{-2}$ [12]. The left figure shows a time range of 30 hours, the right figure shows the first hour only.

Scalp cooling under standard conditions

The model was used for a first investigation of the effects of scalp cooling on local scalp skin concentrations. A standard chemotherapy procedure was modelled, in which the patient receives a total dose of 75 mg m$^{-2}$ doxorubicin, intra–venously administered in a period of 2 hours. The effect of scalp cooling was compared to no cooling. In the scalp cooling case, perfusion to the scalp skin was reduced to 20% during administration of chemotherapy and the subsequent 2 hours, for a total period of 4 hours. The results of these simulations are shown in figure 6.

Blood serum levels are continuously high during the 2 hours of administration, after which they show a rapid fall. The concentration in the scalp skin is a little higher than the blood serum concentration and it stays relatively high for the complete simulation period. Doxorubicin concentration in the scalp is significantly lower when scalp cooling is applied, compared to no scalp cooling. After a certain period, no distinction in scalp skin concentration can be made between the two cases. When no cooling is applied, the maximum concentration in the scalp is equal to 1.66 µg ml$^{-1}$ and the average concentration during the first 24 hours is 0.61 µg ml$^{-1}$. With scalp cooling, the maximum concentration is 0.48 µg ml$^{-1}$ and the average concentration equals 0.38 µg ml$^{-1}$. Thus, reducing the perfusion by a factor of 5, see figure 3, reduces the maximum concentration by a factor of 3.5 and the average concentration by a factor of 1.6. As seen from figure 1, such a reduction can have a notable effect on cell survival.
In a parameter study we investigated some important parameters in the physiologically based pharmacokinetic model for doxorubicin, see also [13]. The effect of these parameters on maximum and average scalp skin concentration during scalp cooling was evaluated. In the simulations, we used a skin temperature of $T = 19.2^\circ C$ and a minimum perfusion value of $\Phi_{\text{min}} = 0.20$. As an example, values used and results for tissue perfusion are shown in table 5. Changes in these perfusion rates are compensated by changing perfusion or volume of the rapidly perfused compartment, such that cardiac output and total body volume of the model remain the same. When the standard deviation was unknown, we used the mean value and a variation of 20% to define the lower and upper limit.

The parameter study [13] shows that the most important parameters influencing maximum doxorubicin concentration in the scalp skin during scalp cooling are the perfusion of both the scalp skin and the liver, the body mass, the body height and the fraction of doxorubicin bound to the blood. Maximum modelled doxorubicin concentration is 0.56 $\mu$g ml$^{-1}$, for an increase in scalp skin perfusion from 0.23 to 0.35 l min$^{-1}$. A decrease in perfusion to 0.23 l min$^{-1}$ results in a concentration of 0.42 g ml$^{-1}$, which is the lowest peak concentration in the parameter study. This influence of perfusion was as expected, since the concentration is flow limited. The influence on average doxorubicin concentration in the scalp skin is a bit lower, however, seeing that results range from 0.35 to 0.40 $\mu$g ml$^{-1}$.
Table 5
Effect of Changes in Tissue Perfusion (W_B) on Maximum Scalp Skin Concentration (C_{max}) and Average Scalp Skin Concentration C_{avg} during Cooling (T = 19.2°C, \Phi_w = 0.27).

<table>
<thead>
<tr>
<th>WB (l min^{-1})</th>
<th>C_{max} (\mu g ml^{-1})</th>
<th>C_{avg} (\mu g ml^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>down up</td>
<td>down up</td>
<td>down up</td>
</tr>
<tr>
<td>Liver</td>
<td>0.25 0.45</td>
<td>0.52 0.45</td>
</tr>
<tr>
<td>Heart</td>
<td>0.18 0.34</td>
<td>0.49 0.47</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.89 1.21</td>
<td>0.50 0.47</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0.25 0.33</td>
<td>0.48 0.48</td>
</tr>
<tr>
<td>Gut</td>
<td>0.95 1.37</td>
<td>0.51 0.46</td>
</tr>
<tr>
<td>Slowly perfused</td>
<td>1.27 1.87</td>
<td>0.50 0.47</td>
</tr>
<tr>
<td>Scalp skin</td>
<td>0.23 0.35</td>
<td>0.42 0.56</td>
</tr>
</tbody>
</table>

Up and down correspond to increasing or decreasing a parameter, respectively. Responses of the model under standard conditions are C_{max} = 0.48 \mu g ml^{-1} and C_{avg} = 0.38 \mu g ml^{-1}

**CONCLUSION AND DISCUSSION**

In this paper, we developed a computational model for mass transport of chemotherapy in the human body during scalp cooling. Doxorubicin is used as a chemotherapeutic agent. In the model, we used a lumped–parameter approach with the assumption that doxorubicin exhibits flow–limited characteristics. Comparisons of the pharmacological model of doxorubicin to plasma concentration data showed that the model was able to predict these concentrations well. Therefore, the model was used to investigate the effect of scalp cooling, especially the effect of reduced tissue perfusion, on local tissue concentrations.

The results of the model show that during scalp cooling, maximum tissue concentrations may be reduced by a factor of 3.5 when perfusion is reduced by a factor of 5. The average concentration was reduced by a factor of 1.6. As illustrated in figure 1, these reductions can have a dramatic influence on cell survival, especially when an additional effect of temperature on metabolism is present. The parameter study showed that important parameters in the model are the perfusion of both the scalp skin and the liver, the body mass and the body height. Other important parameters are the fraction of doxorubicin bound to the blood and the volume of the scalp skin.

One limitation of the pharmacological model used is that the only effect of scalp cooling that is modelled is reduced tissue perfusion. Due to cooling, mass transfer characteristics may change. In a study on the temperature dependent dermal absorption of chloroform, a large decrease in skin permeability with decreasing temperature was found [14]. In our model, the effect of reduced temperature might be modelled using a temperature dependent partition coefficient K_p (see equation 4). For this, however, knowledge of the temperature dependency of these coefficients for doxorubicin is needed. Currently, this data is unavailable. Therefore, any reduced uptake of doxorubicin due to reduced temperature is unaccounted for in the current model. This means that predicted tissue concentrations by the model might be higher than in reality.

In parallel studies, we are now extending the developed model to complete cooling of patients undergoing cardiac surgery with the emphasis on influence of anaesthesia [15,16] and individualised human thermoregulation [17].
REFERENCES