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Heat Exposure and Drugs

A Review of the Effects of Hyperthermia on Pharmacokinetics

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Summary

Acute heat loading is encountered in several everyday situations, during physical exercise or work in a hot climate are just 2 examples. Special forms of heat exposure include different types of steam baths and saunas. External heating induces changes in haemodynamics, body fluid volume and blood flow distribution, which in turn may affect the pharmacokinetics of a drug and the therapeutic response. Documentation of the effects of heat exposure on the pharmacokinetics of drugs in humans is very limited, but based on the documentation some general conclusions can be drawn.

The effects of external heating on absorption and elimination of those orally administered drugs which have been studied (e.g. midazolam, ephedrine, propranolol and tetracycline), have been minor. Systemic absorption of transdermally and subcutaneously administered drugs [insulin, nitroglycerin (glyceryl trinitrate) and nicotine] is in most cases enhanced by external heating, leading to higher plasma drug concentrations.

In general, pharmacokinetic interactions between heat exposure and drug therapy are rare and limited to special situations, in which local blood flow (for example, over the skin) is enhanced many-fold because of hyperthermia. When pharmacodynamics are concerned, in most cases the probability of interactions is low, but in the treatment of malignant tumours hyperthermia may potentiate cytotoxic effects of drugs without enhancement of myelosuppressive effects.

Acute environmental heat load is most commonly encountered during physical exercise in hot environments or short term travels in tropical climate. Some special forms of acute heat exposure are leisure activities such as taking different types of steam baths and saunas, and these are characterised by short term stays at exceptionally high temperature, even up to 100°C. In the chemotherapy of malignant tumours, whole-body hyperthermia, as well as local and regional heating, has been used for the targeting of drug therapy and the enhancing of cytotoxic effects.[1]

The physiology of external heating in humans has been studied under many different conditions, including experiments with water-perfused suits, heat chambers and sauna. Even though there are differences in the intensity and duration of heat exposure in these studies, it has been noted that, for example, the haemodynamic effects induced by different forms of heating are basically analogous. This is discussed briefly in the following section.[2]

1. Physiological Effects of External Heating

1.1 Temperature Regulation, Body Fluid and Electrolyte Balance

During heat exposure thermoregulatory mechanisms are activated within the body, when the skin temperature reaches 40 to 41°C.[3] In a hyperthermia study in 4 individuals wearing water-perfused suits, the skin temperature of these individuals increased from 36.6 to 40.9°C over a period of 40 to 53 minutes, and their mean rectal temperature rose from 37.1 to 38.2°C.[4] In a sauna (air temperature 80 to 90°C), skin temperatures varying between 39.9 and 40.4°C during a 10- to 20-minute heat exposure have been recorded.[5] Body core temperature, measured via the rectum, increase up to 38.1 to 38.7°C after a 20-minute sauna at an air temperature of 80 to 90°C, with oral temperatures of between 37.3 and 39.5°C after 10 to 30 minutes at 80 to 100°C.[5,6] Oesophageal temperature has been reported to increase at a rate of 0.07°C/min between temperatures of 37.6 to 38.0°C, and at a rate from 0.30 to 0.40°C/min between temperatures of 38.0 to 39.0°C in a sauna at 83 to 85°C. It has been suggested that the measurement of oesophageal temperature is a relatively accurate indirect method for measuring core temperature in humans.[7]

The additional thermal load is removed by evaporation and during acute exposure to external temperature of 48°C (aural temperature 37.9 to 38.6°C), bodyweight loss from sweating varies between 0.5 and 0.8 kg/h,[8] and during a sauna at 84°C between 417 and 544g, when an oesophageal temperature of 39.0°C was reached in approximately 20 minutes.[9] Plasma electrolyte changes during a 2-hour heat exposure at 48°C have been minimal, but during a 20-minute heat exposure in a sauna (air temperature 92 to 94°C, rectal temperature 38°C) increased serum sodium and potassium concentrations have been reported.[8,10]

Intensive short term heat exposure first induces a temporary haemodilution and thereafter haemoconcentration, explained by fluid shift between interstitial and intravascular fluid compartments.[11,12] Similarly, at first an initial fall in plasma protein concentration is seen, but this is followed by a linear positive correlation between the duration of heat exposure and total plasma protein and albumin concentrations.[8]

1.2 Haemodynamic Responses

The onset of heat stress leads to several adaptive circulatory events, partly because of direct vasodilatation and partly because of hormonal responses during the heat stress. Cutaneous blood flow is enhanced at a rate of 3 L/min/°C increase in rectal temperature.[13] In practice, external heating induces a 10- to 12-fold increase in skin blood flow, corresponding to more than half of cardiac output.[13] Peripheral vascular resistance is reduced during heat exposure, and cardiac output is increased approximately 2-fold to compensate for the effects of reduced venous return and centrally circulating blood volume on haemodynamics, the effects being mediated by increased sympathetic activity.[2,13]

During experimental hyperthermia (30 to 50 minutes, skin temperature 40.5 to 40.9°C) visceral blood flow to the gastrointestinal tract and kidneys decreases by 30 to 35%.[4,14,15] Similarly, hepatic blood flow, measured by indocyanine green (ICG) clearance, has been shown to decrease by roughly 30% during a 3-hour rest at 105°F (41°C).[16] A short term stay in a sauna (air temperature 85 to 95°C, mean sublingual temperature 37.6°C, 3 • 10 minutes) has been reported to induce a statistically insignificant mean reduction of 17% in ICG clearance.[17]

1.3 Hormonal Responses

Hormonal changes during heat exposure are mainly stress responses to external heating and contribute to the maintenance of thermal homeostasis and electrolyte balance.[18] The plasma concentration of noradrenaline, released from sympathetic nerve endings, is increased approximately 2- to 3-fold during external heating to a skin temperature of 41.5°C as well as during a sauna at 80 to 100°C.[6,13,19] In general, no changes in plasma adrenaline levels are seen.[7,20] Moreover, hyperthermia stimulates secretion of growth hormone and prolactin.[6,21,22] The effects of external heating on plasma levels of other hormones, e.g. cortisol, are more varied and are likely to be related to the somewhat different study design and circadian changes in plasma levels of these hormones.

2. Heat Exposure and Pharmacokinetics

In theory, the abovementioned changes in haemodynamics, body fluid volume and blood flow distribution during external heating may affect drug absorption, distribution and elimination. However, documentation on the effects of hyperthermia on drug pharmacokinetics is very scant. This review is based on studies performed during physical exercise in warm or hot versus exercise in thermoneutral environment, during various forms of external heating (saunas and steam baths) and chemotherapy-related hyperthermia in humans. Studies in patients with infection-induced hyperpyrexia are beyond the scope of this review, because the mechanisms of temperature regulation in hyperpyrexia differ from those of external heating. In addition, individual and sporadic case reports are not discussed in this review because of their more or less anecdotal nature and lack of power when compared with controlled studies. The studies discussed in this review are summarised in tables I and II.

2.1 Drug Absorption

2.1.1 Gastrointestinal Absorption

Both repeated 12 to 15 minutes heat exposure at air temperature of 100°C for 2 hours (rectal temperature 39.1°C) and 2 bouts of 50-minute treadmill exercise at 49°C (rectal temperature 39.5°C) have been reported to delay gastric emptying of water and carbohydrate solution slightly, but not statistically significantly versus rest at room temperature and exercise in a neutral (air temperature 18°C) environment, respectively.[40,41]

The gastrointestinal absorption rate of midazolam 15mg and ephedrine 50mg has been studied in a sauna (air temperature 80 to 100°C) in 6 healthy young females.[34] In the study, the absorption rate of midazolam was slowed statistically significantly, but ephedrine, on the contrary, was absorbed faster, when compared with the administration of the corresponding drugs in a control session at room temperature. Considering that the midazolam segmental area under the concentration-time curve up to 6 hours after administration ($AUC_{0\text{-}6h}$) and plasma concentrations were reduced during a sauna, but no difference in the $AUC_{0\text{-}\infty}$ was seen, it can be concluded that the overall absorption and bioavailability of midazolam remained unchanged.[34] Plasma concentrations of ephedrine were transiently increased in the study, which is in line with the higher absorption rate observed.

In another study with midazolam, neither its bioavailability nor absorption rate were affected by heat exposure in a sauna (air temperature 85 to 100°C) in 6 young healthy male volunteers.[36] In spite of that, the peak plasma drug concentration after single dose administration (C_{max}) of mid-

Table I. Studies on the effects of hyperthermia on pharmacokinetics

Drug	Dose and route	n	Design	Source of heat	Reference
Nitroglycerin (glyceryl trinitrate)	10mg transdermal patch	12 (9 m, 3 f)	Open, randomised, crossover	Sauna	23
Methyl salicylate	5g percuteneously	6 (6 m)	Open, randomised, crossover	Rest/bicycle ergometer exercise in hot environment	24
Carboplatin	300 mg/m^2 body surface IV	6 (6 f) for pk	Open, non-randomised	Deep abdominal hyperthermia by an applicator	25
Clonidine	6mg transdermal patch	8 (8 m)	Open, randomised, crossover	Hot bath, ambient temperature	26
Cisplatin	60 mg/m^2 (n=2), 80 mg/m^2 (n=1) IV	3 (3 m)	Open, non-randomised	Water-perfused suit	27
Labelled rapid-acting insulin	10IU subcutaneously	8 (8 m)	Open, randomised, crossover	Sauna	28
Labelled intermediate-acting insulin	8IU subcutaneously	8 (8 m)	Open, randomised, crossover	Sauna	29
Carboplatin	100-575 mg/m^2 IV	17 (gender not given) for pk	Open, non-randomised	External body heating by a heating system	30
Melphalan	15-20 mg/m^2 IV	10 (gender not given) for pk	Open, randomised, crossover	External body heating by a heating system	31
Insulin	Individual therapeutic doses subcutaneously	9 (9 m)	Open, randomised, crossover	Bicycle ergometer exercise in a temperature-regulated cabin	32
Theophylline	200 mg/m^2 orally in solution	6 (6 m)	Open, randomised, crossover	Bicycle ergometer exercise in a temperature-controlled room	33
Ephedrine Midazolam	50mg tablet 15mg tablet	6 (6 f)	Placebo-controlled, double-blind, randomised, crossover	Sauna	34
Propranolol	40mg tablet	8 (2 m, 6 f)	Placebo-controlled, double-blind, randomised, crossover	Sauna	35
Midazolam	15mg tablet, 0.05 mg/kg IV	6 (6 m)	Open, randomised, crossover	Sauna	36
Nicotine	10 mg/16h + 15 mg/16h transdermal patches (total nicotine content 41.5mg)	12 (7 m, 5 f)	Open, randomised, crossover	Sauna	37
Tetracycline	500mg tablet	8 (5 m, 3 f)	Open, randomised, crossover	Sauna	38
Carboplatin Ifosfamide	480 mg/m^2 IV 5 g/m^2 IV	6 (3 m, 3 f) for pk	Open, non-randomised	Extracorporal heating of blood by haemodialyser	39

Abbreviations: IV = intravenously administered; n = number of participants; f = female; m = male; pk = pharmacokinetic.

azolam was higher and midazolam plasma concentrations were transiently increased compared with the control session at 22°C. Similar results of higher C_{max} and transiently increased plasma concentrations of propranolol have been reported in an almost identical (air temperature 85 to 100°C) sauna setup.[35] However, no changes in drug pharmacodynamics were observed in these studies, and the drug concentrations equalled those of respective control sessions during the post-sauna period.[35,36]

The effects of short term heat exposure on gastrointestinal drug absorption are contradictory, but the tendency seems to be that no marked changes in absorption rate or bioavailability of drugs are seen. Judging from the pharmacodynamic data, in those cases in which some pharmacokinetic changes have been reported, their clinical signifi-

Table II. Results of the studies on hyperthermia and pharmacokinetics

Drug	Dose and route	Ambient/body temperature	Duration	Main results	Reference
Carboplatin	100-575 mg/m^2 IV	Body: 41.8°C *vs* normothermia	60 min	V_{ss} ↑, $t_{½\alpha}$, % of dose in 24-h urine ↓, CL, V_c, Vd β and $t_{½\beta}$ ↔	30
	60-80 mg/m^2 IV	Body: 42-42.3°C *vs* 37°C	2h	C_{max} , $t_{½\beta}$ ↔	27
	300 mg/m^2 IP	Systemic: 38.2°C Tumour: 41.0°C *vs* normothermia	≥ 45 min	AUC-ratio peritoneal fluid/plasma (↓), % of dose in 24-h urine (↓), no statistical analysis	25
	480 mg/m^2 IV	Body: 41.8°C *vs* 37°C	60 min	AUC and C_{max} ↑	39
Clonidine	6mg transdermal patch	Hot bath (40°C) *vs* room temperature	5 min	C_{max}, $t_{½\beta}$, $AUC_{0\text{-}168h}$, urinary excretion in 168 h and plasma concentrations ↔	26
		Hot weather *vs* cold weather, ambient air temperatures not given	not given	C_{max}, $t_{½\beta}$, $AUC_{0\text{-}168h}$ and urinary excretion (0-168 h) ↔, plasma concentrations ↑	
Ephedrine	50mg orally	Air: 80-100°C *vs* 22°C	10 min x 3, separated by 10-min cooling periods	Absorption rate ↑, t_{max} ↓, C_{max}, $AUC_{0\text{-}6h}$ and $AUC_{0\text{-}\infty}$ ↔	34
Nitroglycerin (glyceryl trinitrate)	10mg transdermal patch	Air: 90°C (skin 38°C) *vs* room temperature	20 min	Plasma concentrations ↑	23
Ifosfamide	5 g/m^2 IV	Body: 41.8°C *vs* 37°C	60 min	AUC ↓, C_{max} (IFO, 4-OH-IFO) ↓(?), $t_{½\beta}$ ↔	39
Insulin: rapid-acting	10IU subcutaneously	Air: 85°C *vs* 22°C	25 min x 2, separated by 5-min cooling period	Disappearance of ^{125}I -insulin from injection site ↑	28,29
Insulin: intermediate-acting	8IU subcutaneously	Air: 85°C *vs* 22°C	25 min x 2, separated by 5-min cooling period	Disappearance of ^{125}I -insulin from injection site ↔	29
Insulin: rapid- and intermediate-acting	Individual therapeutic dose subcutaneously	Air: 30°C rest/exercise (skin 34.2°C) *vs* 10°C rest/exercise	Bicycle ergometer performance 15 min x 3, separated by 5-min rest periods	Plasma free insulin ↑, AUC of plasma free insulin ↑	32
Melphalan	15-20 mg/m^2 IV	Body: 41.8°C *vs* normothermia	60 min	V_{ss} , V_c , CL, $t_{½\alpha}$ and $t_{½\beta}$ ↔	31
Methyl salicylate	5g percutaneously	Air: 40°C rest/exercise *vs* 22°C rest/exercise	6h, exercise 45 min each hour for 6h	Rest and exercise at 40°C: plasma concentrations ↑, cumulative urinary excretion (0-8 h) ↑, $AUC_{0\text{-}5h}$ ↑	24
Midazolam	15mg orally	Air: 80-100°C *vs* 22°C	10 min x 3, separated by 10-min cooling periods	Absorption rate ↓, V_{ss}/f_{PO} ↑, $AUC_{0\text{-}6h}$ ↓, $AUC_{0\text{-}\infty}$ ↔	34
	15mg orally 0.05 mg/kg IV	Air: 85-100°C *vs* 22°C	10 min x 4, separated by 5-15-min cooling periods	Orally: C_{max} ↑, $t_{½\beta}$ ↑, $AUC_{0\text{-}2h}$ ↑, $AUC_{0\text{-}\infty}$ ↔ IV: V_{ss} , CL ↔	36
Nicotine	15 mg/16 h + 10 mg/16 h patches total nicotine content 41.5mg)	Air: 77-84°C *vs* 23°C	10 min x 3, separated by 5-min cooling periods	C_{max} ↑, amount absorbed ↑, plasma concentrations in sauna ↑, $AUC_{0\text{-}1h}$ ↑, $AUC_{0\text{-}3h}$ ↔	37

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Table II. Contd

Drug	Dose and route	Ambient/body temperature	Duration	Main results	Reference
Propranolol	40mg orally	Air: 85-100°C *vs* 22°C	10 min x 3, separated by 5-min cooling periods	C_{max} ↑, plasma concentrations in sauna ↑, AUC_{0-5h} ↑, AUC_{0-24h} ↔	35
Tetracycline	500mg orally	Air: 76-87°C *vs* 22°C	10 min x 3, separated by 5-min cooling periods	C_{max} and AUC_{0-24h} ↔, urinary excretion (0-2 h) ↓, urinary excretion (0-24 h) ↔	36
Theophylline	200 mg/m^2 orally in solution	Air: 40°C exercise *vs* 22°C rest/exercise	2h	$t_{½\beta}$ ↑, Vd ↓, CL ↓, $AUC_{0-\infty}$ ↑, plasma concentrations ↔	33

Abbreviations and symbols: AUC = area under plasma concentration-time curve; CL = clearance; C_{max} = maximum plasma concentration; IFO = ifosfamide; IP = intraperitoneally; IV = intravenously; 4-OH-IFO = 4-hydroxy-ifosfamide; t_{max} = time of C_{max}; $t_{½\alpha}$ = distribution half-life; $t_{½\beta}$ = elimination half-life; V_{ss}/f_{PO}; V_c = central compartment volume of distribution; Vd = volume of distribution; Vdβ = terminal phase apparent volume of distribution; ↑ = increased/ prolonged; ↓ = decreased/shortened; ↔ = no change *vs* respective control session.

cance has been minor. Thus, short term hyperthermia is unlikely to possess any major effects on gastric absorption of otherwise readily absorbable drugs.

2.1.2 Transdermal and Subcutaneous Absorption

Marked enhancement of cutaneous blood flow during heat exposure may, in turn, affect the pharmacokinetics of transdermally and subcutaneously administered drugs, and the majority of the studies focusing on pharmacokinetics and heat exposure have been performed with these routes of administration. The drugs that have been studied include insulin, nitroglycerin, nicotine, methyl salicylate and clonidine.

Both rest and bicycle ergometer exercise at 30°C (mean skin temperature 34.2°C) increased plasma free insulin concentrations and free insulin AUC statistically significantly compared with the respective values at 10°C after subcutaneous administration of rapid- and intermediate-acting insulin in 9 patients with insulin-dependent diabetes mellitus.[32] In a sauna (air temperature 85°C), subcutaneous absorption of ^{125}I-labelled rapid-acting insulin was accelerated statistical significantly (110%) in 8 males with insulin-dependent diabetes mellitus during two 25-minute stays in the sauna, when compared with absorption rates at room temperature (22°C).[28] In addition, in both studies the accelerated insulin absorption induced a statistically significant fall in blood glucose levels when compared with the control session without the sauna.[28,32] However, the sauna had no effects on the absorption of amorphous insulin when compared with an identical sauna setup at 85°C, it was suggested by the author that the effects of external heating on the pharmacokinetics of amorphous and soluble insulin differ from each another.[29] In principle, faster insulin absorption and hypoglycaemia are more likely to occur after the injection of rapid-acting soluble insulin than after amorphous intermediate-acting insulin before heat exposure. In order to avoid the symptoms of hypoglycaemia during and after heat exposure, a small reduction in insulin dose or an extra snack may be warranted as a precaution for patients using rapid-acting insulin.[28]

Plasma nitroglycerin concentrations have been studied in 12 healthy volunteers (aged 28 to 63 years) by using transdermal nitroglycerin patches 10mg during a 20-minute sauna (air temperature 90°C, peak skin temperature 39°C).[23] In the study, the mean plasma concentrations of nitroglycerin increased significantly from 2.3 to 7.3 nmol/L during heat exposure when compared with a control session at room temperature. At the same time, a statistically significant fall in diastolic blood pressure and a significant increase in heart rate was recorded, and 9 of the 12 volunteers reported headache as an adverse effect. It was suggested that the increased transdermal uptake of nitroglycerin

was partly due to an enhanced blood flow resulting from heat-induced subcutaneous vasodilatation.[23]

The relationship between blood flow and the transdermal absorption of nitroglycerin has been demonstrated in a study[42] in which nitroglycerin patches applied to an area of the upper arm were heated locally by infrared light for 15 minutes. In the study, infrared heating enhanced local blood perfusion, measured by photoplethysmography, and at the same time, plasma nitorglycerin concentrations were significantly increased. Correspondingly, the cooling off of the patch area was followed by a fall in plasma nitroglycerin concentrations.[42]

The effects of heat exposure on the pharmacokinetics of transdermal nicotine have been studied in a sauna (air temperature 77 to 84°C) in 12 healthy volunteers who smoked.[37] Two transdermal nicotine patches (total nicotine content 41.5mg) were applied to the lateral aspect of an arm of the volunteer 5 hours before heat exposure. The heat exposure consisted of three 10-minute stays in a sauna separated by two 5-minute cooling periods at 23°C. Having a sauna increased the mean plasma nicotine concentrations significantly compared with the control session at 23°C. However, after the heat exposure the plasma nicotine concentrations gradually decreased to equal those of the pre-sauna period. In addition, the amount of nicotine remaining in the patches was measured after the removal of the patches; after the sauna session the concentration was significantly lower than after the control session, a sign that higher amount of nicotine were released from the patch in the sauna.

Exposure to air temperatures of 40°C has been shown to increase the systemic availability of methyl salicylate.[24] In a crossover design, methyl salicylate 5g was smeared over the skin on the chests of 6 males, and plasma and urine salicylate concentrations were then measured for 5 and 8 hours, respectively. The participants followed a crossover protocol, in which they were at rest or performed physical exercise (45 minutes each hour for 6 hours at 30% of maximal oxygen consumption) at 22 and 40°C. Plasma salicylate concentrations were statistically significantly increased during exercise and rest at 40°C, when compared with rest and exercise at 22°C. The AUC of methyl salicylate was not calculated in the study, but the plasma concentration *vs* time data strongly suggests that the overall absorption of methyl salicylate was augmented by heat exposure. In addition, at rest the cumulative urinary excretion of methyl salicylate was significantly higher at 40°C than at 22°C.

In a recent study, a hot bath (5 minutes in a bath with a water temperature of 40°C) had no effects on maximum plasma concentrations, AUC or urinary excretion of transdermally administered α-adrenoceptor agonist clonidine. A patch containing clonidine 6mg was applied on the right side of the chest of 8 healthy volunteers in a study performed during winter with and without bathing and during summer without bathing.[26] Bathing induced no changes in plasma clonidine concentrations. Nevertheless, the authors noted that plasma concentrations of clonidine tended to be higher during hot weather, but neither the ambient temperatures of the winter and summer trials or the individual skin temperatures were given in the paper. Despite somewhat higher clonidine concentrations in summer, no differences in blood pressure or heart rate were seen between the winter and summer trials.

In most studies of transdermal and subcutaneous drug administration, total drug absorption and plasma drug concentrations have increased during heat exposure. The phenomenon seems to be mainly related to heat-induced local vasodilatation and acceleration of skin blood flow.[23,42] In addition, changes in the physicochemical properties of transdermal patches, sweating and increased humidity of the skin may contribute to the release and diffusion of transdermally administered drugs. The 1.5- to 2.5-fold increases in plasma drug concentrations seen in some studies suggest that the possibility of heat-drug interactions should be taken into account, while using transdermal and subcutaneous administration at temperatures higher than 30°C.

2.2 Drug Distribution

The effects of physical exercise in a hot environment (30% of maximal oxygen uptake, air temperature 40°C) on the pharmacokinetics of oral theophylline solution (200 mg/m^2 body surface) have been studied in 6 young, healthy non-smoking volunteers during 2 hours of exercise on an ergometric bicycle.[33] The volume of distribution (Vd) of theophylline was statistically significantly reduced by exercise at 40°C *vs* rest at 22°C. Since exercise of the same intensity performed at 22°C had no effect on Vd of theophylline, the authors concluded that the reduction was related to dehydration during the exercise protocol.

During short term heat exposure in a sauna the Vd of midazolam was reported to increase because of the hot environment in 1 study.[34] However, no effects of external heating on the Vd of ephedrine, ICG or midazolam have been seen in analogous studies.[17,34,36]

In a phase I study in 13 patients with advanced/metastatic malignancy, whole-body hyperthermia (41.8°C) for 1 hour increased the steady-state volume of distribution (V_{ss}) of intravenously administered escalating doses of carboplatin (100 to 575 mg/m^2 body surface).[30] Plasma protein binding, central compartment Vd and terminal phase apparent Vd were not affected in the study by whole-body heating. This indicates that the distribution of carboplatin was not significantly affected. The change of V_{ss} was not discussed further, and it may have been incidental or, at least in theory, because of a better perfusion and higher tissue binding of carboplatin to tissues of low perfusion rate during euthermia. In a randomised study with an identical setup by the same research group, the Vd of melphalan (15, 17.5 and 20 mg/m^2) was unaffected.[31]

In studies with combined chemotherapy and whole-body hyperthermia, no major effects on plasma drug concentration and AUCs have been seen. In a pilot study in 3 patients with inoperable advanced refractory malignancies, the patients received *cis*-diamminedichloroplatinum II (cisplatin) chemotherapy (80 mg/m^2, n = 2; 60 mg/m^2 n = 1) during hyperthermia.[27] The patients were heated up to a core temperature of 42 to 42.3°C by water-perfused suits, and hyperthermia was maintained for 2 hours. Plasma total and ultrafiltrable platinum concentrations were roughly identical with or without heating, but no statistical analysis was performed, probably because of the small sample size. Even though the study had to be discontinued because of renal toxicity, the authors noted that pharmacokinetic data did not explain the severe nephrotoxicity encountered in the patients.[27] In another study, the $AUC_{0\text{-}24h}$ of intravenous carboplatin 480 mg/m^2 was also significantly reduced by heating, but its peak plasma concentration was, on the contrary, significantly higher.

Regional abdomino-pelvic hyperthermia in 6 patients with ovarian cancer resulted in a reduction of the peritoneal AUC/plasma AUC ratio of carboplatin 300 mg/m^2 administered intraperitoneally.[25] The data suggest more rapid clearance of carboplatin from the peritoneum during hyperthermia, which may have been related to enhanced blood flow of tumour tissue due to heat-induced blood flow redistribution, since the average temperature of tumour tissue was clearly higher (41.0°C) than maximal systemic temperature of normal tissue (38.2°C) during the 45-minute heating. However no statistical analysis of the results was made in the study.

Hyperthermia lasting for several hours may lead to excessive dehydration and by that manner reduce the Vd of a drug significantly. In practice that may reduce the Vd of drugs that are not highly lipid-soluble and have small Vd, for example, corresponding to blood volume. The available data suggest that the effects of short term (≤ 1 hour) heat exposure on drug distribution are negligible. An explanation for this can be that the loss of body water, and enhanced perfusion of otherwise less-perfused tissues because of circulatory hyperkinesia, oppose each other's effects on drug distribution. In the case of carboplatin, plasma protein binding was not affected by heat and it is plausible to assume that protein binding is not a major factor affecting drug distribution during hyperthermia.

2.3 Drug Elimination

2.3.1 Hepatic Metabolism

The metabolism of drugs with high hepatic extraction rate can be considered as flow-dependent and sensitive to changes in hepatic blood flow.[43] In principle, heat exposure can reduce hepatic blood flow as a result of blood flow redistribution and reduced blood flow to the internal organs. Direct measurement of human hepatic blood flow during external heating is complicated in most cases, and indirect clearance methods using ICG clearance for hepatic blood flow measurement have usually been applied. ICG clearance has been demonstrated to decrease by roughly 30% during 3-hour rest at 105°F (41°C).[16] A short term stay in a sauna (85 to 95°C, 3 • 10 minutes) induced a mean reduction of 17% in ICG clearance, but the observed reduction was not statistically significant.[17]

The elimination half-life of theophylline was prolonged significantly (from 6.4 hours at rest to 8.0 hours during exercise) in a hot environment (40°C).[33] At the same time, the plasma clearance of theophylline was significantly reduced, which is in agreement with the prolongation of theophylline elimination half-life. Even though the authors suggested that the effects on theophylline elimination could have been related to a reduction of hepatic blood flow, it must be noted here that theophylline is a drug of low hepatic extraction and its clearance and elimination should not be greatly affected by changes in hepatic blood flow.

As well as hepatic blood flow, hepatic enzyme activity contributes to the hepatic clearance of high-extraction drugs, and an increase in ambient temperature may be reflected as enhanced enzyme-catalysed reactions.[44] The effects of heat exposure on hepatic metabolism of midazolam have been studied during a sauna. Midazolam undergoes extensive first-pass metabolism by hepatic CYP3A isoenzymes.[45,46] The clearance of midazolam remained unaltered in 2 studies, implying that midazolam removal from the plasma compartment was unaffected by heat exposure.[34,36]

Furthermore, heat exposure had no effects on α-hydroxymidazolam plasma concentrations or on α-hydroxy midazolam/midazolam AUC-ratio either after intravenous or oral midazolam administration.[35] On the basis of the results it was assumed that CYP3A-mediated hepatic first-pass metabolism and the capacity to metabolise midazolam were not affected by intensive short term heat exposure. Since there are no data available on the effects of hyperthermia on other CYP isoenzymes and on other hepatic enzymes in man, it is not plausible to expand the conclusions to them.

In a study by Wiedemann et al.,[39] the peak plasma concentrations of intravenous ifosfamide 5 g/m^2 and its metabolite 4-hydroxy-ifosfamide (4-OH-IFO) were significantly lower when the 6 patients were treated with blood temperatures of 41.8°C compared with 37°C, but no change in the elimination half-life of ifosfamide was observed. Hyperthermia was achieved by haemodialysis and the difference in plasma concentrations was because of the loss of drug by haemodialysis, which also explains the lower $AUC_{0\text{-}24h}$ of ifosfamide and its hydroxy-metabolite.

In conclusion, hepatic blood flow is reduced during longer-lasting (1 to 3 hours) heat exposure, which in turn may reduce the hepatic clearance of drugs with high hepatic extraction rates. Intensive short term heat exposure (< 1 hour) is unlikely to induce any effects on hepatic blood flow or on CYP3A-mediated hepatic metabolism.

2.3.2 Renal Excretion

At high temperatures renal blood flow is decreased, which, together with dehydration and body water-conserving hormonal mechanisms, reduces urine output.[12,47] In healthy volunteers, renal elimination of drugs which are mainly or to a considerable amount excreted unchanged into urine has been studied with ephedrine and tetracycline.[34,38] Plasma clearance of a single oral dose of ephedrine 50mg was not affected by a sauna (85 to 100°C) in 6 healthy female volunteers, but urinary excretion of ephedrine was not measured in the study.[34] Urinary tetracycline excretion after an oral 500mg dose of tetracycline was transiently

decreased in 8 healthy individuals immediately after the heat exposure in a sauna (76 to 87°C) *vs* a control group at room temperature, but the total tetracycline excretion during the 24-hour collection period remained unaffected.[38] A temporary reduction in tetracycline excretion was not reflected in the tetracycline plasma concentrations or AUC in the study.

The renal excretion of carboplatin has been evaluated in 3 separate clinical studies in patients with malignant tumours. After intravenous administration, renal excretion of escalating doses of carboplatin was statistically significantly reduced by hyperthermia during the 24-hour urine collection period.[30] The authors concluded that the decrease was related to either late excretion of carboplatin or, most probably, to incomplete urine collection. The latter explanation seems to be more acceptable, since carboplatin clearance was not affected by heat exposure. Furthermore, the therapeutic index of carboplatin was increased, but there was no enhancement of myelosuppression, and the authors concluded that carboplatin in combination with hyperthermia may provide new insights into cancer chemotherapy.

In another study, on average a higher fraction of carboplatin was excreted into the urine after intraperitoneal administration during abdomino-pelvic hyperthermia than without heating.[25] However, a statistical analysis was not presented in the study, and on the basis of presented standard deviation data, the difference may not have reached statistical significance. The response to treatment was enhanced in platinum sensitive patients, and it was concluded that those patients could benefit from the combined treatment.

Furthermore, the unchanged urinary clearance of carboplatin during 41.8°C whole-body hyperthermia has been reported in a pilot study in 3 patients with refractory sarcoma or malignant teratoma.[27] The study was discontinued because of renal toxicity, but the authors noted that the pharmacokinetic data did not explain the severe nephrotoxicity encountered in the patients.

The effects of 41.8°C whole-body heating on pharmacokinetics of melphalan, a renally excreted alkylating antitumour agent, were not affected in 10 patients with advanced or metastatic malignancy.[31] The study revealed no change in clearance or elimination half-life of melphalan, when compared to normothermia, indicating that its renal excretion was unchanged. Again, the synergistic effects of whole-body hyperthermia and chemotherapy were observed in the study, but because of the induction of myeloprotective cytokines, myelosuppression was not enhanced in relation to the enhancement of cytotoxic effects.

In principle, renal drug excretion may be reduced at high ambient temperature because of the decreased renal blood flow and dehydration. In the case of tetracycline, reduced drug excretion had no effect on plasma drug concentrations, and heat-induced changes in renal drug clearance may be of very limited clinical importance in most cases.

3. Concluding Remarks

There are several limitations to the interpretation of the studies discussed. Depending on the main interest of the investigators, the setup of the studies varies largely, for example, when duration and intensity of external heating are concerned. In addition, various methods (e.g. rectal, skin and esophageal temperature) have been used as markers of body core temperature, or the actual body temperature has not been mentioned in the paper at all. The number of individuals is very limited in some of the studies, and thus, the results of these studies can be considered more or less suggestive of nature. Furthermore, the populations studied are very heterogeneous, including a number of healthy individuals along with the patient groups.

However, it must be noted that very few studies and limited data on the effects of heat exposure on pharmacokinetics in humans exist, and, therefore, it was considered appropriate to include all the presented studies in this review. The main points of heat exposure and pharmacokinetics are summarised below.

During heat exposure, hepatic, renal and visceral blood flow are reduced and skin blood flow enhanced because of the redistribution of organ blood flow. Despite the adaptive changes in blood flow distribution and body-fluid balance, the effects of heat exposure on the pharmacokinetics of orally administered drugs are likely to be of minor clinical importance. In healthy volunteers, the effects of external heating on gastric absorption, distribution and hepatic and renal drug elimination tend to be clinically insignificant. On the other hand, the route of drug administration is the most important determinant affecting pharmacokinetics during heat exposure. The pharmacokinetics of transdermally and subcutaneously administered drugs are most likely to be affected by heat exposure, since external heating has been shown to enhance transdermal and subcutaneous drug absorption and increase plasma drug concentrations in several studies. Thus, the possibility of heat-drug interaction should be taken into account when using the transdermal and subcutaneous routes of drug administration at temperatures higher than 30°C.

In patients treated with the combination of hyperthermia and chemotherapy, no consistent changes in drug pharmacokinetics have been seen. Interestingly, the cytotoxicity of these drug may be enhanced despite the lack of pharmacokinetic changes, and in addition, heat exposure may reduce myelosuppressive effects of these drugs in some patients as well. Hyperthermia combined with chemotherapy may have potential benefits in the treatment of some patients.

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