Metabolic effects of i.v. propacetamol, metamizol or external cooling in critically ill febrile sedated patients

B. POBLETE, J.-A. ROMAND, C. PICHARD, P. KÖNIG AND P. M. SUTER

Summary

We have measured the metabolic response to sequential administration of propacetamol, metamizol and/or external cooling in 20 febrile patients under sedation and analgesia and during mechanical ventilation. There was no change in temperature (T) after propacetamol therapy, whereas after metamizol only a small decrease was noted (from 38.9 (SEM 0.2) to 38.5 (0.3) °C; P=0.02). External cooling produced a significant decrease in T (39.1 (0.2) to 37.1 (0.2) °C; P=0.0001) accompanied by a decrease in energy expenditure (EE) (2034 (73) to 1791 (88) kcal day⁻¹, P<0.004). Heart rate and minute ventilation decreased significantly in parallel. There were no other changes in haemodynamics or pulmonary gas exchanges. We conclude that propacetamol and metamizol did not produce a clinically significant decrease in T in febrile ICU patients whereas external cooling decreased both T and EE. The parallel decrease in body temperature and EE seemed to be related to opioid administration or sedation, or both. (Br. J. Anaesth. 1997; 78: 23–127).

Key words

Fever in critically ill patients is related frequently to either the systemic inflammatory response syndrome (SIRS) or infection. Usually fever is treated with antipyretic drugs, often paracetamol or metamizol. External cooling by different methods, such as sponging the body surface with ice-cooled water, is also used. Indeed, a previous study in critically ill patients demonstrated diminished oxygen consumption related to decreased body temperature improving the oxygen demand–delivery ratio. However, body cooling in healthy humans results in shivering which increases energy expenditure (EE).

The aim of this study was to measure EE as an integrated indicator of body metabolic activity after reduction in temperature. Our hypothesis was that external cooling may induce an increase in EE, in contrast with drugs which, by resetting the thermoregulatory set point, decrease EE. Therefore, we designed a prospective, unblinded, crossover study to evaluate the respective effects of centrally acting drugs (propacetamol or metamizol) or external physical cooling in febrile ICU patients.

Patients and methods

The study was approved by the Ethics Committee of our institution. The requirement for informed consent was waived by the committee who judged that the therapies were applied independently by the attending physician and were accepted in clinical practice, and no invasive measurements were made.

We studied 20 patients undergoing mechanical ventilation via a tracheal tube, with a rectal temperature greater than 38.5 °C and in whom the physician in charge wished to decrease fever. No patient had an inspired oxygen fraction greater than 0.6, a pneumothorax or a broncho-pleural fistula. Patients’ lungs were ventilated with a Veolar-Hamilton (Hamilton Bonaduz, Switzerland) or Engström-Erica ventilator (Engström, Bromma, Sweden). Ventilatory settings, adjusted to obtain normal arterial blood-gas tensions, were maintained constant during the study. No patient received a caloric intake exceeding the measured EE at baseline. Analgesia and sedation were adjusted to obtain clinical comfort of the patient, as judged by nurses and physicians, by a continuous and constant infusion of morphine 2–6 mg h⁻¹ and midazolam 2–10 mg h⁻¹ to obtain a sedation level of 3–4, according to the score of Ramsay and colleagues. Patients were kept supine during the study.

The following variables were monitored continuously: rectal temperature, heart rate and arterial pressure, ventilatory frequency, tidal volume; inspired and expired minute ventilation were recorded from the ventilators. Oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were also measured continuously by indirect calorimetry.
(Deltatrac, Datex Instrumentation Corp., Helsinki, Finland) and EE was recorded and calculated using a modified De Weir formula. Shivering was assessed continuously by the nurse and investigators. Arterial blood-gas tensions were measured intermittently with Stat profile (Nova Biomedical, Boston, MA, USA).

TREATMENT DESIGN
The aim of the study was to measure the metabolic response to reduction in temperature induced by different therapeutic means. There was no randomization at enrolment of patients or of therapy sequence chosen, because the choice of treatment was decided independently by the physician in charge of the patient and not by the investigator. Three different antipyretic therapies used currently in our unit were prescribed: i.v. bolus administration of propacetamol 1000 mg or metamizol 500 mg, or external cooling with cloths plunged into iced water and placed on most of the body surface. Cloths were changed every 15–30 min. In case of failure of the first treatment, a second and, if necessary, a third treatment were given until the desired temperature was obtained. Treatment was considered to have failed if temperature either increased or decreased <1 °C in the 60 min after administration of therapy.

METABOLIC MEASUREMENTS AND CALIBRATION
Before and after measurements, the Deltatrac metabolic monitor was calibrated for room air according to the manufacturer’s instructions. Calibration for atmospheric pressure and a standard gas blend containing 95% oxygen and 5% carbon dioxide was also carried out before measurements began. The Deltatrac metabolic monitor is an open system containing 95% oxygen and 5% carbon dioxide was also calculated as $\dot{V}_{CO_2}$ divided by the respiratory quotient (RQ) where $RQ = (1 - \dot{V}_{O_2}) / (\dot{V}_{O_2} - \dot{V}_{CO_2})$. A baseline steady state (baseline 0) was established for each patient. Steady state was defined as a stable $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and EE (<10% changes from preceding values) during at least 10 min. Thereafter, the first antipyretic therapy was given.

Before changing to alternative treatment, all variables were recorded and assumed as the new baselines (baseline 1 or 2) for the subsequent therapeutic manoeuvre. The final measurement was recorded under metabolic steady state conditions as defined above.

STATISTICAL ANALYSIS
Data were compared between different therapies (propacetamol, metamizol and external cooling) using one-way analysis of variance; when a significant difference was seen, the Tukey–Kramer multiple comparisons test was used. The paired $t$ test was also used to compare treatment effects with their respective baseline conditions. GraphPad InStat 2.0 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Data are expressed as mean (SEM).

Results
We studied 20 patients (four females), mean age 47 (range 17–79) yr. Admission diagnosis, treatment expired and diluted expired gas. The carbon dioxide fractions are measured with an infrared carbon dioxide sensor (CX 104, Datex Instrumentation Corp, Helsinki, Finland); the difference between the inspired and expired oxygen fractions is measured with a differential paramagnetic oxygen sensor (OM 101, Datex Instrumentation Corp, Helsinki, Finland). $\dot{V}_{CO_2}$ is calculated as the product of the carbon dioxide fraction in the diluted expiratory flow and a constant flow of 45 litre min$^{-1}$. $\dot{V}_{O_2}$ is calculated as $\dot{V}_{CO_2}$ divided by the respiratory quotient (RQ) where $RQ = (1 - \dot{V}_{O_2}) / (\dot{V}_{O_2} - \dot{V}_{CO_2})$. A baseline steady state (baseline 0) was established for each patient. Steady state was defined as a stable $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and EE (<10% changes from preceding values) during at least 10 min. Thereafter, the first antipyretic therapy was given.

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Results
We studied 20 patients (four females), mean age 47 (range 17–79) yr. Admission diagnosis, treatment

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (yr)/sex</th>
<th>Diagnosis</th>
<th>Amines</th>
<th>Antibiotics</th>
<th>APACHE score</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>67/M</td>
<td>Abdominal trauma/SIRS</td>
<td>—</td>
<td>Yes</td>
<td>36</td>
<td>S</td>
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<tr>
<td>2</td>
<td>65/M</td>
<td>Aortic dissection/SIRS</td>
<td>—</td>
<td>Yes</td>
<td>32</td>
<td>S</td>
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<tr>
<td>3</td>
<td>79/M</td>
<td>ARDS</td>
<td>—</td>
<td>No</td>
<td>28</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>51/M</td>
<td>Aspiration pneumonia</td>
<td>—</td>
<td>No</td>
<td>18</td>
<td>S</td>
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<tr>
<td>5</td>
<td>62/M</td>
<td>Cerebral ischaemia after ACB</td>
<td>—</td>
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<td>12</td>
<td>S</td>
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<tr>
<td>6</td>
<td>18/M</td>
<td>Head trauma</td>
<td>NA</td>
<td>No</td>
<td>15</td>
<td>S</td>
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<tr>
<td>7</td>
<td>47/M</td>
<td>Head trauma</td>
<td>NA</td>
<td>Yes</td>
<td>17</td>
<td>S</td>
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<tr>
<td>8</td>
<td>17/M</td>
<td>Head trauma</td>
<td>—</td>
<td>No</td>
<td>27</td>
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<tr>
<td>9</td>
<td>44/M</td>
<td>Head trauma/aspiration pneumonia</td>
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<td>No</td>
<td>19</td>
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<tr>
<td>10</td>
<td>72/M</td>
<td>Ileus/SIRS</td>
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<td>No</td>
<td>9</td>
<td>S</td>
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<tr>
<td>11</td>
<td>19/M</td>
<td>Multiple trauma/ARDS</td>
<td>—</td>
<td>Yes</td>
<td>32</td>
<td>S</td>
</tr>
<tr>
<td>12</td>
<td>36/M</td>
<td>Multiple trauma/aspiration pneumonia</td>
<td>—</td>
<td>Yes</td>
<td>5</td>
<td>S</td>
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<tr>
<td>13</td>
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<td>Multiple trauma/septic shock</td>
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<td>Yes</td>
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<td>14</td>
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<tr>
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<td>68/F</td>
<td>Perforated sigmoid colon</td>
<td>A</td>
<td>Yes</td>
<td>20</td>
<td>S</td>
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<tr>
<td>16</td>
<td>24/M</td>
<td>Pneumonia</td>
<td>—</td>
<td>No</td>
<td>23</td>
<td>S</td>
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<tr>
<td>17</td>
<td>21/M</td>
<td>Rhabdomyolysis, hypoxic encephalopathy</td>
<td>—</td>
<td>Yes</td>
<td>32</td>
<td>S</td>
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<tr>
<td>18</td>
<td>56/F</td>
<td>SIRS after oesophageal resection</td>
<td>—</td>
<td>Yes</td>
<td>23</td>
<td>S</td>
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<tr>
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<td>61/F</td>
<td>Tracheo-oesophageal fistula</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>D</td>
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<tr>
<td>20</td>
<td>71/F</td>
<td>Urosepsis</td>
<td>A, Dobut</td>
<td>Yes</td>
<td>17</td>
<td>S</td>
</tr>
</tbody>
</table>
outcome and Apache II score are listed in table 1. At the end of the study, data from one patient (No. 17) were excluded from the final analysis. This patient suffered from rhabdomyolysis and hypoxic encephalopathy and therefore received no sedation/analgesia to allow continuous neurological evaluation/surveillance. He developed an important encephalopathy and therefore received no sedation.

Synchronized intermittent mandatory ventilation (SIMV) was used in eight patients; in 10 patients ventilation comprised pressure support mode (PS) and positive end-expiratory pressure (PEEP), and in one patient volume controlled mode was used. Only one patient (No. 7) received a neuromuscular blocking agent for controlled hyperventilation. In parallel with the decrease in body temperature, minute oxygen ventilation decreased significantly (from 14.7 (1) to 13.1 (0.9) litre min⁻¹; P<0.02), but arterial oxygen saturation (SaO₂) from 94 (1) % to 95 (1) %, the quotient relating arterial partial pressure of oxygen and inspired oxygen fraction (PaO₂/FiO₂) from 203 (19) mm Hg to 190 (17) mm Hg and arterial pH (from 7.39 (0.01) to 7.39 (0.01)) did not change significantly. Patients continuously received either enteral (n=7) or parenteral (n=4) nutrition, or a combination of both (n=3), or no nutritional support (n=5).

**METABOLIC RESULTS**

Treatment sequence is shown in table 2. Fourteen patients who first received i.v. drugs needed more than one treatment to decrease body temperature. In contrast, in five of six patients external cooling significantly decreased temperature. In four patients body temperature was controlled either by metamizol (n=2) or by a combination of paracetamol and external cooling. Temperature, haemodynamic and metabolic variables at baseline and after treatment are shown in table 3. During baseline measurements, mean percentage of random variation was 1.8 (6.7) % (median 0.0%; lower and upper 95% confidence intervals −2.3% and +5.8%, respectively). There were no differences between baselines 0, 1 and 2 for all study variables. Temperature did not change significantly after administration of propacetamol.

Metamizol resulted in a statistically significant but clinically irrelevant decrease in temperature from 38.9 (0.2) to 38.5 (0.3) °C (P=0.02). In contrast, application of external cooling decreased temperature from 39.1 (0.2) to 37.1 (0.2) °C (P<0.0001). There were no clinical signs of shivering with either therapy.

Treatment with metamizol or external cooling decreased heart rate significantly (P=0.0043 and P<0.0001, respectively), but no significant change was observed after administration of propacetamol (P=0.14).

Five patients received vasopressor infusions to maintain adequate systemic arterial pressure, and in three (Nos 6, 7 and 15) the dose of these agents was reduced during the study. In two other patients (Nos 9 and 20) no change in noradrenaline infusion was made. Table 3 demonstrates that excluding the three patients in whom the catecholamine dose was modified did not significantly influence the metabolic changes induced by the different treatments.

Administration of propacetamol and metamizol did not significantly change mean values of EE (P=0.35 and P=0.41, respectively). However,
external cooling decreased EE significantly from 2034 (73) to 1791 88 kcal day$^{-1}$ ($P=0.004$). Metabolic variations calculated as percentage changes from baseline are summarized in table 3. Mean $\dot{V}_{O_2}$ decreased by 12.6 (3.3) % and $\dot{V}_{CO_2}$ by 10.9 (4.3) % during external cooling.

Figure 1 shows individual percentage variation in EE from baseline for treatment with propacetamol, metamizol and external cooling. There was wide variability among patients' responses to the treatments with propacetamol and metamizol. However, in patients treated with external cooling, EE decreased by 6.1–36% from baseline in 17 patients; in two patients (Nos 14 and 13) EE increased by 7.9% and 15.3%, respectively.

Discussion

Twenty febrile ICU patients were prospectively enrolled to compare the respective effects of antipyretic drugs (propacetamol or metamizol) or physical (external cooling) therapies on body temperature and metabolic variables using indirect calorimetry. The major finding was a decrease in EE related to a decrease in body temperature in patients treated by external cooling, whereas treatment by propacetamol or metamizol did not induce a clinically relevant decrease in body temperature.

External cooling is thought to have no effect on the thermoregulatory setpoint.$^{6-8}$ Furthermore, it is generally admitted that a physiological response to cold stress is shivering$^2$ to maintain core temperature. Therefore, in response to external cooling, EE could either vary independently of $T$ or increase with diminution of body temperature. Our findings did not confirm our hypothesis that external cooling did not affect or increase metabolic rate. The association between a decrease in both body temperature and EE could be because of the absence of a compensatory homeostatic response. This physiological response was most probably blunted by morphine or sedation with midazolam, or both.$^9-12$ This possibility is fully supported by the fact that patient No. 17 was excluded because he developed a shivering-equivalent reaction with increased EE while not receiving opioids as he required close neurological surveillance. This observation further supports our hypothesis that in the absence of sedation or analgesia, increased EE is expected during external cooling. A similar observation was also reported by Manthous and colleagues.$^3$ Indeed, shivering is suppressed by general anaesthetics, centrally acting agents such as clonidine and especially by opioids such as pethidine, morphine and fentanyl.$^10$

In clinical practice, although controversial, antipyretic therapy is often prescribed to combat temperatures greater than 38.5°C. Indeed, fever complements the host immunological defence against invasion by micro-organisms. However, when a decrease in body temperature seems clinically important then paracetamol or metamizol are often prescribed. Drug-induced antipyrexia is preferred because it is easier than application of iced sponges and has proved to be efficient in paediatric studies.$^{13-15}$ Our study has demonstrated that external cooling, under sedation–analgesia conditions, is a valuable means of decreasing temperature with a concomitant decrease in oxygen consumption. The 12% decrease in oxygen consumption in externally cooled patients matched previously published data reporting a 5–7% change in metabolism per 1°C change in temperature.$^{16}$ Thus even though the benefit of decreasing fever is debatable, decreasing EE and oxygen consumption may be clinically relevant in patients lacking coronary artery oxygen delivery reserve experiencing a septic episode or severely hypoxaemic.

The limitations of the study are that first, the treatment sequence was not randomized, but the physician in charge of the patient was proposed a random sequence of treatment by the investigators and the final decision left to him. This procedure may have introduced possible bias into the study. Second, to minimize spontaneous changes in body temperature not related to the treatment procedure, there was no washout period between i.v. drug administrations, which may have resulted in some overlapping between treatments. However, from a clinical viewpoint, if 2 h after administration of treatment no clinically relevant effect is observed, then therapy is usually considered to have failed, leading to administration of another form of therapy. Finally, these effects were not caused by variations in pH, nutrition or ventilation, or by changes in sedation or analgesia (tables 2, 3).
We conclude that propacetamol and metamizol administration had no observable effect on fever in critically ill patients under analgesia and sedation, whereas external cooling efficiently decreased body temperature and metabolic demands.

Acknowledgements

Financial support was received from Sandoz Nutrition, Switzerland.

References