Inotropic and Vasoactive Drug Treatment of Interleukin 2 Induced Hypotension in Sheep

Stuart Zeilender, Donald Davis, R. Paul Fairman, and Frederick L. Glauser

Pulmonary Division, Medical College of Virginia/McGuire Veterans Administration Hospitals, Richmond, Virginia 23298-0050

ABSTRACT

The side effects associated with recombinant interleukin 2 administration, including systemic hypotension and a vascular leak syndrome, may limit therapy before reaching maximum doses of this innovative and promising treatment for cancer. In an attempt to reverse this hypotension without decreasing cardiac output and systemic oxygen delivery ($D_{O_2}$), we studied several inotropic agents, dobutamine, dopamine, amrinone, CaCl$_2$, and a pure $\alpha$-adrenergic vasoconstrictor, methoxamine. These were administered singly or in combination to sheep with chronically implanted arterial and pulmonary artery catheters following 24 h of 3 x 10$^6$ units/kg recombinant interleukin 2. Compared to baseline values, 24 h of recombinant interleukin 2 infusion caused a significant increase in cardiac output from 4.4 ± 0.9 (SD) to 5.0 ± 0.6 liters/min, a significant fall in systemic vascular resistance (SVR) from 21 ± 7 to 15 ± 5 units, a decrease in mean systemic blood pressure (SBP) from 88 ± 9 to 78 ± 6 mm Hg, and a decrease in left ventricular stroke work from 51.5 ± 8 to 49 ± 6 gram meters ($P < 0.05$) without any change in $D_{O_2}$. Dobutamine, dopamine, and CaCl$_2$ returned SBP to baseline values by increasing cardiac output without increasing SVR. Methoxamine increased SBP by increasing SVR, but cardiac output decreased significantly. A combination of 12 μg/kg/min of dopamine and 2 to 3 mg of methoxamine infused over 15 min resulted in an increase in SBP, cardiac output, and SVR to baseline values while maintaining $D_{O_2}$ and oxygen consumption ($V_{O_2}$). We suggest that this latter combination would be appropriate for clinical use since it returns physiological parameters to normal.

INTRODUCTION

Administration i.v. of rIL-2 with or without so called lymphokine activated killer cells is a new treatment for patients with far advanced cancer (1–8). Early results have been encouraging. Some series report up to a 50% partial or complete remission rate (1–9). However, rIL-2 infusion is associated with multiple side effects, including systemic hypotension and a vascular leak syndrome (1–15), which often necessitate decreasing or discontinuing therapy. Originally, the systemic hypotension was thought to be due to intravascular volume depletion from the vascular leak syndrome. However, in recent clinical reports, a decrease in SVR, SBP, and LVSW and an increase in cardiac output have been found within 2 h to 5 days in patients receiving bolus infusions of rIL-2 with or without concomitant administration of lymphokine activated killer cells (12–15). Whether these changes are due to rIL-2 directly, release of vasoactive cytokines by rIL-2, or cofactors such as administration of such drugs as acetaminophen or indomethacin for fever and chills, ranitidine for prophylaxis against gastrointestinal bleeding, hydroxyzine for pruritus, and parenteral meperidine for shaking chills, which most patients receive (3, 7–12), is unclear. Treatment of the hypotension remains empiric and consists of administering inotropic and vasoactive drugs such as dopamine and/or phenylephrine with i.v. fluids and/or decreasing or discontinuing rIL-2 administration (3, 7–12).

We have previously shown that in a sheep model (16–18) in which 9 x 10$^6$ units/kg total dose of rIL-2 (without other concomitant medication) is administered continuously over 3 days, there is a predictable fall in SVR, increase in cardiac output, and decrease in SBP beginning at 24 h which parallels the findings in humans. The present study was designed to identify a drug regimen that could be administered to reverse these changes without adversely affecting cardiac output, oxygen delivery ($D_{O_2}$), oxygen consumption ($V_{O_2}$), oxygen extraction, or LVSW.

MATERIALS AND METHODS

Pilot Studies

The dose of each inotropic and/or vasoactive medication (see below) was determined in normal sheep by performing dose-response curves beginning with the lowest dose recommended for humans (19, 20). The final dose chosen for the inotropic agents and methoxamine was that which increased cardiac output and SVR at least 15%, respectively, over baseline values. Amrinone in dosages varying from 10 to 40 μg/kg/min had no effect on baseline cardiac output. An arbitrary dose of 20 μg/kg/min was chosen to determine if amrinone was effective during rIL-2 infusion.

To determine if the sequence of administration of various inotropic/vasoactive agents and combinations (see below) affected hemodynamic responses (see below), the following sequence of drugs was administered over a 3-day period in one sheep: Day 1 (see below for dosage), dopamine and methoxamine, methoxamine, CaCl$_2$, amrinone, dobutamine, and dopamine. Between the administration of each drug all parameters were allowed to return to baseline values before the next drug was administered. Day 2, amrinone, CaCl$_2$, dopamine, methoxamine, dobutamine, and dopamine plus methoxamine. On Day 3 the order of drugs given on Day 1 was reversed. Evaluation of these data revealed no more than a 7% variation between sequences for SBP, PAP, RAP, PWP, cardiac output, SVR, LVSW, RVSW, arterial blood gases, and arterial oxygen saturation. However, the Day 1 sequence took 6.5 h to complete; Day 2, 5.5 h; and Day 3, 4.5 h. We thus used the Day 3 sequence since these experiments were the shortest to complete.

Experimental Design

Ten sheep (Sheep 1–10) weighing 30–35 kg were lightly anesthetized with 30 mg/kg Surital i.v. A balloon tipped flow directed catheter was inserted into the pulmonary artery under pressure monitoring. A carotid artery catheter was inserted percutaneously. The animal was returned to its cage and allowed to awaken. The next day the animal was placed in a body sling in a special cage and allowed free access to food and water. Baseline measurements (termed “baseline control”) of SBP, PAP, RAP, PWP, cardiac output, SVR, LVSW, RVSW, arterial blood gases, and arterial oxygen saturation were determined in normal sheep by performing dose-response curves beginning with the lowest dose recommended for humans (19, 20). The final dose chosen for the inotropic agents and methoxamine was that which increased cardiac output and SVR at least 15%, respectively, over baseline values. Amrinone in dosages varying from 10 to 40 μg/kg/min had no effect on baseline cardiac output. An arbitrary dose of 20 μg/kg/min was chosen to determine if amrinone was effective during rIL-2 infusion.
of these two is reported as “baseline rIL-2.” The rIL-2 infusion was continued and the following drugs were administered i.v. in the following dosage and sequence.

Inotropic Agent. (a) Ten ml of 10% CaCl$_2$ were infused over 15 min followed by measurement of the above parameters. CaCl$_2$ was chosen because raising extracellular levels may cause an influx of calcium into cells. Intracellular calcium is important in modulating myocardial contractility and peripheral arterial vasoconstriction; (b) dopamine, 12 µg/kg/min over 15 min, β-adrenergic and dopaminergic agent; (c) amrinone, 20 µg/kg/min over 15 min, phosphodiesterase inhibitor; (d) dobutamine, 15 µg/kg/min over 15 min, β-adrenergic agent.

Vasoactive Agent. Methoxamine, 3–5 mg over 15 min, pure α-adrenergic vasoconstrictor.

Combination. Dopamine, 12 µg/kg/min, and methoxamine, 2–3 mg, over 15 min. Between the administration of each drug all parameters were allowed to return to baseline values before the next drug was administered.

Additional Studies

To determine if IL-2 and the dopamine/methoxamine combination affected the oxygen consumption ($V_O_2$, $D_O_2$), or oxygen extraction, we studied five additional sheep (Sheep 11–15) and prepared them in the above manner. We determined $D_O_2$, $V_O_2$, and $O_2$ extraction during baseline control, during “baseline rIL-2,” and at the end of a 15-min infusion of 12 µg/kg/min dopamine and 2–3 mg methoxamine.

Calculations

\[
SVR = \frac{SBP - RAP}{CO} = \text{Units}
\]

\[
D_O_2 = \frac{CO \times CaO_2}{ml/min}
\]

\[
CaO_2 = (Hb \times \% \text{ arterial O}_2 \text{ saturation}) + 0.003 PaO_2
\]

\[
V_O_2 = CO \times (CaO_2 - CvO_2)
\]

\[
CvO_2 = (Hb \times \% \text{ mixed venous O}_2 \text{ saturation}) + 0.003 PO_2
\]

\[
O_2 \text{ extraction} = \frac{V_O_2}{D_O_2} = \%
\]

\[
LVSW = \frac{CO/HR \times systolic BP - PWP \times 0.0136}{g.m}
\]

\[
RVSW = \frac{CO/HR \times systolic PAP - RAP \times 0.0136}{g.m}
\]

in which CO is cardiac output, CaO$_2$ is content of oxygen in the arterial blood, Hb is hemoglobin, CvO$_2$ is content of oxygen in mixed venous blood, BP is blood pressure, and HR is heart rate.

Vascular pressures were recorded on a Hewlett Packard physiological recorder. Thermodilution cardiac output was performed using a Lyons cardiac output machine. Arterial blood gases and saturation were determined on an IL blood gas analyzer.

Statistics

Analysis of variance using a Stat Pack program on an Apple desk top computer was used. When a significant difference was found a paired t test was used. Values are reported as means ± SD. Baseline rIL-2 values were compared to baseline control values. All treatment values are compared to baseline rIL-2 values. $P < 0.05$ was considered significant.

RESULTS

Induced and Derived Hemodynamics (Sheep 1–10) (Table 1). After 24 h of rIL-2 infusion, there was a significant fall in SVR and SBP and a significant increase in cardiac output and HR compared to baseline control values ($P < 0.05$). There was a significant fall in LVSW, but not RVSW, after 24 h of rIL-2 infusion compared to baseline control values.

CaCl$_2$, dopamine, and dobutamine all increased SBP and cardiac output to baseline control values. Amrinone had no effect. SVR was unaffected by any of these agents and only dobutamine increased PAP significantly ($P < 0.05$). Dopamine and dobutamine increased HR significantly compared to baseline control and baseline rIL-2 values. Methoxamine increased SBP and SVR significantly and caused a significant fall in cardiac output compared to baseline control and baseline rIL-2 values. In contrast, cardiac output was maintained at baseline rIL-2 levels, and SVR, SBP, and LVSW were increased significantly when dopamine and methoxamine were administered together.

Arterial Blood Gases and $D_O_2$ (Sheep 1–10) (Table 2). Arterial blood gases were not changed by 24 h of rIL-2 infusion. There was no change for PaO$_2$, PaCO$_2$, and pH in any of the drug groups. In contrast, $D_O_2$ was increased by dobutamine infusion whereas methoxamine administration significantly decreased $D_O_2$ compared to baseline control and baseline rIL-2 values.

$D_O_2$, $V_O_2$, and $O_2$ Extraction (Sheep 11–15) (Table 3). $V_O_2$ was similar in control baseline, control rIL-2, and the methoxamine/dopamine groups. $O_2$ extraction fell significantly in baseline rIL-2 as compared to baseline control. There was no significant difference between the methoxamine + dopamine and baseline rIL-2 $O_2$ extraction. Compared to baseline control values, $D_O_2$ tended to increase with rIL-2 and methoxamine + dopamine administration, although these trends were not statistically significant.

DISCUSSION

In this sheep model, i.v. administration of rIL-2 is associated with a fall in SVR, SBP, and LVSW and a concomitant increase in cardiac output. Although the sequence of these physiological changes is not known, we postulate that the decreased SVR is a primary event. The reduction of afterload permits an increase in cardiac output. However, this increase is not enough to maintain SBP and systemic hypotension results. These findings are similar to those reported in patients receiving rIL-2 and in septic patients (9–13, 15). Even though the cardiac output is high in septic patients, myocardial depression is present since the left ventricular ejection fraction falls, and heart rate and left ventricular end diastolic volumes increase. We feel that our model also displays some degree of myocardial depression since the heart rate increases as the cardiac output rises and LVSW falls significantly (Table 1) after 24 h of rIL-2 infusion.

Whether rIL-2 itself or some mediator(s) causes the peripheral vasodilation and myocardial depression is not known. rIL-2 increases the developed isometric tension of the isolated rat right atria after coincubation with either arachidonic acid or calcium ionophore 23187 (21). In contrast, in the isolated perfused working rat heart there was no change in cardiac output, coronary flow, or cellular morphology at the end of a 1-h infusion of 1, 100, or 1000 units/ml of IL-2 (22). Additionally, rIL-2 does not directly alter endothelial function as evidenced by the application of rIL-2 to endothelial cell monolayers. Albumin flux as a reflection of increased permeability does not increase (23).

It is possible that the myocardial depression and peripheral vasodilation may be due to rIL-2 induced release of vasoactive cytokines such as tumor necrosis factor and/or interleukin 1. It is known that endotoxin administration is associated with increased blood levels of tumor necrosis factor which could mediate the cardiac output increase and SBP and SVR decrease (24–28). Additionally, tumor necrosis factor infusion leads to many of the hemodynamic changes found with sepsis, endotoxemia, and rIL-2 infusion (24, 25). The “final” common pathway for the depressed myocardial function and peripheral vasodia-
INOTROPIC AND VASOACTIVE DRUG TREATMENT OF IL-2 INDUCED HYPOTENSION

Table 1 rIL-2 induced and derived hemodynamic changes (Sheep 1–10): response to inotropic and vasoactive agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline control</th>
<th>Baseline rIL-2</th>
<th>Dopamine†</th>
<th>Dobutamine</th>
<th>Amrinone</th>
<th>CaCl2</th>
<th>Methoxamine</th>
<th>Methoxamine + dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>88 ± 9†</td>
<td>78 ± 6†</td>
<td>91 ± 4†</td>
<td>92 ± 13*</td>
<td>77 ± 1</td>
<td>87 ± 16§</td>
<td>104 ± 17†</td>
<td>100 ± 10†</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.4 ± 0.9</td>
<td>5.0 ± 0.6‡</td>
<td>6.0 ± 2</td>
<td>7.0 ± 2‡</td>
<td>5.0 ± 1</td>
<td>6.1 ± 0.8</td>
<td>3.0 ± 0.5‡</td>
<td>5.0 ± 2</td>
</tr>
<tr>
<td>SVR (units)</td>
<td>21 ± 7</td>
<td>15 ± 5</td>
<td>15 ± 5</td>
<td>14 ± 6</td>
<td>14 ± 6</td>
<td>14 ± 5</td>
<td>25 ± 5</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>14.4 ± 2.5</td>
<td>16.6 ± 1.5</td>
<td>17.0 ± 6</td>
<td>24.0 ± 5.2‡</td>
<td>16.4 ± 3.1</td>
<td>18.8 ± 3.6</td>
<td>19.6 ± 2.1</td>
<td>19.6 ± 2.1</td>
</tr>
<tr>
<td>PWP (mm Hg)</td>
<td>7.6 ± 1.8</td>
<td>8.4 ± 1.8</td>
<td>7.4 ± 1.8</td>
<td>11.2 ± 6.0</td>
<td>7.8 ± 1.3</td>
<td>8.5 ± 1.3</td>
<td>9.8 ± 1.3</td>
<td>9.8 ± 1.3</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>104 ± 20</td>
<td>125 ± 18*</td>
<td>156 ± 22</td>
<td>286 ± 46*</td>
<td>141 ± 7</td>
<td>133 ± 18</td>
<td>115 ± 13*</td>
<td>115 ± 13*</td>
</tr>
<tr>
<td>LVSW (g.m)</td>
<td>51.5 ± 8</td>
<td>40 ± 6†</td>
<td>55 ± 6</td>
<td>36 ± 7*</td>
<td>43.4 ± 9</td>
<td>62.4 ± 12</td>
<td>65 ± 7*</td>
<td>13.6 ± 1.7</td>
</tr>
<tr>
<td>RVSW (g.m)</td>
<td>9.8 ± 1.1</td>
<td>10.9 ± 2</td>
<td>9.8 ± 3.5</td>
<td>18.3 ± 3.6*</td>
<td>9.6 ± 1</td>
<td>13.7 ± 4</td>
<td>13.6 ± 1.7</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD.
† P < 0.05 compared to baseline control.
‡ P < 0.05 compared to baseline control.
§ P < 0.05 compared to baseline control.
¶ P < 0.05 compared to baseline control.

Table 2 rIL-2 induced changes in PaO2 and oxygen delivery (D02) (Sheep 1–10): response to inotropic and vasoactive agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline control</th>
<th>Baseline rIL-2</th>
<th>Dobutamine</th>
<th>Amrinone</th>
<th>CaCl2</th>
<th>Methoxamine</th>
<th>Methoxamine + dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (torr)</td>
<td>103 ± 3*</td>
<td>105 ± 4</td>
<td>105 ± 5</td>
<td>104 ± 5</td>
<td>101 ± 6</td>
<td>101 ± 7</td>
<td>103 ± 5</td>
</tr>
<tr>
<td>D02 (ml/min)</td>
<td>610 ± 128</td>
<td>697 ± 139</td>
<td>868 ± 167</td>
<td>728 ± 167</td>
<td>615 ± 140</td>
<td>420 ± 71‡</td>
<td>700 ± 140</td>
</tr>
</tbody>
</table>

* Mean ± SD.
† P < 0.05 compared to baseline IL-2.
‡ P < 0.05 compared to baseline control.

Table 3 rIL-2 induced changes in D02, VO2, and oxygen extraction (O2 Ext): Sheep 11–15

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline control</th>
<th>Baseline rIL-2</th>
<th>Methoxamine</th>
<th>Methoxamine + dopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>D02 (ml/min)</td>
<td>771 ± 86*</td>
<td>883 ± 118</td>
<td>925 ± 210</td>
<td></td>
</tr>
<tr>
<td>VO2 (ml/min)</td>
<td>126 ± 18</td>
<td>116 ± 24</td>
<td>113 ± 30</td>
<td></td>
</tr>
<tr>
<td>O2 Ext (%)</td>
<td>16.3 ± 2.2</td>
<td>12.4 ± 0.5§</td>
<td>12.2 ± 2.5</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± SD.
§ P < 0.05 compared to baseline control.

The drug of choice. Thus, if one clinically tolerable (Table 1). Although CaCl2 was used in this study, it is potentially more dangerous than the other drugs because of its multiplicity of effects and its tendency to cause conduction abnormalities and arrhythmias (32). Thus, if one were to use a single inotropic drug, dopamine would probably be the drug of choice.

However, none of the inotropic agents reversed the low SVR and, in fact, most caused a further small, nonsignificant fall (Table 1). For this reason we administered a pure α-adrenergic drug (methoxamine) alone. At the dose used (3 to 5 mg infused over 15 min) this drug significantly increased SVR. However, this increase in afterload was associated with a marked fall in CO and a decrease in D02 (Table 2), both clinically undesirable events.

A more “physiological” approach to reverse the rIL-2 induced hypotension might be to combine an inotropic drug, such as dopamine, with low doses of an α-adrenergic vasoconstrictor thus maintaining D02 while simultaneously increasing SVR and SBP. This proved true when using the combination of dopamine and methoxamine. In one additional study (data not shown) this combination of drugs given over 3 days was not associated with tachyphylaxis. In additional studies this combination of methoxamine and dopamine had no adverse effects on VO2 (Table 3). O2 extraction did fall from baseline values with rIL-2 and dopamine/methoxamine administration, but since the D02 tended to increase, overall VO2 remained stable. Thus, we could not find any deleterious effects of the dopamine and methoxamine combination on DO2, or VO2.

Although the combination of methoxamine and dopamine did not have an adverse effect on DO2, or VO2, it is possible that this drug combination could be associated with altered or decreased peripheral tissue perfusion. One sign of inadequate perfusion would be the development of an anion gap metabolic acidosis from lactic acidosis. Calculation of the anion gap in all our groups revealed no increase. In addition, the combination of methoxamine and dopamine at the doses we used could lead to selective decreases in renal perfusion. We did not evaluate this possibility directly, but if this combination is used in patients, total intake and outputs, urine electrolytes, and urine osmolality should be checked at least daily to be sure that renal perfusion is adequate.

One would expect PWP to fall if a vascular leak were present, but in our study PWP remained stable during rIL-2 infusion. However, our animals received 1 liter of i.v. fluids/day in addition to ad libitum p.o. intake and this may have maintained intravascular volume. Even if intravascular volume had decreased, some degree of myocardial dysfunction may have elevated PWP to the normal range. There is a dearth of data regarding PWP measurements in humans receiving rIL-2. In one case example (9) PWP rose significantly during rIL-2 infusion, but the volume of administered fluid was not given. In another study Silverman et al. (11) reported a fall in PWP from 6 ± 2.9 to 3.4 ± 2.6 mm Hg (P < 0.001). The 9 patients in this study received 30 μg/kg of IL-2 as a bolus i.v. infusion every 8 h for 5 days. Following i.v. fluid administration the PWP increased to 8.3 ± 4.8 mm Hg (P < 0.001). Thus, findings in humans are variable and may depend not only upon the degree and amount of myocardial depression present, the presence of a vascular leak, the dose and duration of rIL-2 therapy...
but also upon the amount and timing of fluid replacement.

In conclusion, our results suggest that the rIL-2 induced decreased SVR and SBP can be overcome by a trial of medium dose dopamine and low dose methoxamine (2–3 mg over 15 min) without impairing CO, $D_O$, or $V_O$.

REFERENCES

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