Desflurane and sevoflurane elimination kinetics and recovery quality in horses

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OBJECTIVE
To evaluate pharmacokinetics, recovery times, and recovery quality in horses anesthetized with 1.2 times the minimum alveolar concentration of sevoflurane or desflurane.

ANIMALS
6 healthy adult horses.

PROCEDURES
Anesthesia was maintained with sevoflurane or desflurane for 2 hours at 1.2 times the minimum alveolar concentration. Horses recovered without assistance. During recovery, end-tidal gas samples were collected until horses spontaneously moved. Anesthetic concentrations were measured by use of gas chromatography. After a 1-week washout period, horses were anesthetized with the other inhalation agent. Video recordings of anesthetic recovery were evaluated for recovery quality on the basis of a visual analogue scale by investigators who were unaware of the anesthetic administered. Anesthetic washout curves were fit to a 2-compartment kinetic model with multivariate nonlinear regression. Normally distributed interval data were analyzed by means of paired Student t tests; ordinal or nonnormally distributed data were analyzed by means of Wilcoxon signed rank tests.

RESULTS
Horses recovered from both anesthetics without major injuries. Results for subjective recovery evaluations did not differ between anesthetics. Area under the elimination curve was significantly smaller and time to standing recovery was significantly less for desflurane than for sevoflurane, although distribution and elimination constants did not differ significantly between anesthetics.

CONCLUSIONS AND CLINICAL RELEVANCE
Differences in area under elimination curve between anesthetics indicated more rapid clearance for desflurane than for sevoflurane in horses, as predicted by anesthetic blood solubility differences in this species. More rapid elimination kinetics was associated with faster recovery times, but no association with improved subjective recovery quality was detected. (Am J Vet Res 2015;76:201–207)
the distribution of anesthetic molecules between the blood and gas phases at equilibrium⁵), and CO is cardiac output. Anesthetic elimination, and by extension recovery from anesthesia, should be hastened by use of drugs with a low blood-gas partition coefficient.⁷ In horses, the blood-gas partition coefficient is 0.537 for desflurane and 0.648 for sevoflurane.⁸ Consequently, all else being equal, desflurane should be cleared more rapidly than sevoflurane in horses.

We hypothesized that pharmacokinetic models would reveal a faster washout of desflurane than sevoflurane in horses recovering from constant-dose anesthesia maintained for 2 hours. We also hypothesized that desflurane would be associated with faster recovery times and better subjective recovery quality with less dysphoria, fewer head slaps or head bangs against the floor, and less ataxia than after anesthesia with sevoflurane.

Materials and Methods

ANIMALS

Six adult horses (4 geldings and 2 mares; 2 Arabians, 2 Thoroughbreds, 1 Quarter Horse, and 1 Standardbred) with a mean ± SD age of 17 ± 8 years and body weight of 519 ± 46 kg were enrolled in the study. The number of horses was determined by use of power analysis estimates on the basis of treatment effect sizes and SE estimates from another pharmacokinetic study⁹ on the use of inhalation anesthetics in horses. The study was approved by the Institutional Animal Care and Use Committee at the University of California-Davis.

STUDY DESIGN

The order of anesthetic administration (sevoflurane or desflurane) was randomized with a random number table. Anesthesia was maintained for 2 hours by administration of sevoflurane⁶ (end-tidal concentration, 3.41%) or desflurane⁶ (end-tidal concentration, 9.67%), which was equivalent to 1.2 times the MAC for each agent.⁸ After a washout period of at least 1 week, horses were anesthetized by administration of the other inhalation anesthetic.

PREMEDICATION, ANESTHETIC INDUCTION, AND INSTRUMENTATION

Food, but not water, was withheld from horses prior to the study. A catheter was aseptically placed in a jugular vein of each horse, and the mouth of each horse was rinsed with water. Horses were sedated with dexmedetomidine⁶ (3 µg/kg, IV). Anesthesia was induced with guaifenesin⁶ (50 mg/kg) plus propofol⁶ (3 mg/kg, IV).³ Horses were endotracheally intubated and positioned in left lateral recumbency on a padded table, and anesthesia was maintained with the designated inhalation anesthetic at 1.2 MAC. Lactated Ringer’s solution was administered (5 mL/kg/h, IV).

Esophageal temperature was monitored with a calibrated thermistor, and normothermia was maintained with heat lamps. Blood pressure was measured with an arterial catheter and a pressure transducer calibrated against a mercury manometer (adjusted at the level of the manubrium) and connected to an anesthesia monitor.¹ Dobutamine hydrochloride⁶ was infused at a rate sufficient to maintain MAP between 70 and 80 mm Hg; dobutamine was discontinued if MAP was > 80 mm Hg. Heart rate was monitored via ECG. The PaO₂ and PaCO₂ were measured via an automated gas analyzer,⁶ with accuracy verified daily by use of gas chromatography. The PetCO₂ and concentrations of anesthetic gases were monitored by use of a multigas analyzer,⁶ with gas samples collected from a port near the distal end of the endotracheal tube. Mechanical ventilation to 20 cm H₂O peak pressure was used to maintain PetCO₂ between 35 and 45 mm Hg, and inhalation vaporizers and flowmeters were adjusted to maintain end-tidal anesthetic concentrations constant at 1.2 MAC. All instrumentation was completed within 30 minutes after induction of anesthesia.

ANESTHETIC MAINTENANCE AND RECOVERY

One hour after the start of constant-dose inhalation anesthesia (total anesthesia time, 1.5 hours), atipamezole¹⁰ (60 µg/kg) was administered IV over a 3-minute period to eliminate effects of the α₂-adrenoreceptor agonist dexmedetomidine on the pharmacokinetics of inhalation anesthetics. Dexmedetomidine decreases desflurane MAC¹⁵ and reduces cardiac output.¹⁴ In horses, these effects are completely reversed by administration of atipamezole at a dose > 16 to 20 times the administered medetomidine β-isomer dose.¹⁰ Inhilation anesthetic concentration was maintained constant for the next 60 minutes (equal to 2 hours of constant-dose inhalation anesthesia).

At 100 minutes of constant-dose inhalation anesthesia (total anesthesia time, 130 minutes), instruments were removed from the horses; horses then were transitioned to spontaneous ventilation by allowing PetCO₂ to increase. Vaporizer settings and oxygen flow rates were adjusted accordingly to maintain constant end-tidal anesthetic concentrations. The bladder was drained by temporary placement of a urinary catheter. Horses were moved, while still connected to the breathing circuit, to a 3.5 × 2.75-m padded recovery stall; horses remained in left lateral recumbency for kinetics monitoring and video recording during recovery.

After 2 hours of constant anesthesia (total anesthesia time, 2.5 hours), the endotracheal tube was disconnected from the breathing circuit, and end-expired gas samples were manually collected each minute by use of glass syringes from a sampling port that extended to the distal end of the endotracheal tube. Arterial respiratory gas tensions were measured in blood samples collected from a catheter in an auricular artery every 3 minutes during the first 9 minutes of washout to assess oxygenation and ventilation during recovery. Collection of samples was stopped once horses spontaneously moved their head or limbs. End-tidal anesthetic concentrations were analyzed by direct injection from
were administered 1 breath/min by use of a Hudson helmet. Horses with a respiratory rate

dible with tape, and horses were fitted with a padded

tance. The endotracheal tube was secured to the man-

ning the range of concentrations for the study were
described as a function of \( FE: F_0 \) versus time, where \( FE \)

is the end-tidal (estimating alveolar) concentration of
the anesthetic agent at various points during recov-
er and \( F_0 \) is the end-tidal concentration of anesthetic
agent measured immediately before discontinuation
of maintenance anesthesia. Because \( F_E \) and \( F_0 \) have
the same units, their ratio is a dimensionless quan-
ty. By means of nonlinear least squares regression
with parameters estimated by sequential quadratic
programming,\(^1\) individual washout curves for each
agent and insufflation treatment were fit to an expo-
nential decay model of the following general form:

\[
FE:F_0 = \sum (A_i e^{-\alpha t})
\]

where \( A_i \) is the intercept of the semilogarithmic alve-
olar anesthetic fraction ratio versus time profile of a
compartment, \( t \) is the ith term in the equation, \( e \) is
the natural logarithm, \( \alpha \) is the slope of the semilogarithm-
ic alveolar anesthetic fraction ratio versus time of a
compartment, and \( t \) is time. Terms were added to the
model in a stepwise manner to achieve minimization
of the Akaike information criterion, which was calcu-
lated as follows:\(^2\):

\[
\text{Akaike information criterion} = (n \cdot \log(\text{RSS}/n)) + 2p
\]

where \( n \) is the sample size, \( \text{RSS} \) is the residual sum
of squares in the model, and \( p \) is the number of inde-
pendently adjusted model parameters. Model fit was
evaluated on the basis of a plot of residuals versus
time. Pharmacokinetic parameters for each noncom-
partmental equation were calculated from standard
equations,\(^\text{15} \) with initial data obtained from previous
sevoflurane washout curves in horses.\(^3\)

The VAS scores for the 2 observers were plotted
against each other, and a Pearson product-moment
correlation coefficient was calculated to determine
the extent to which they were correlated. After con-
firming relative agreement, raw VAS scores for 1 inves-
tigator were transformed to the scale of the second via
Passing-Bablok regression.\(^9\) The mean of these scores
was then calculated to generate a single VAS recovery
score per horse per treatment for analysis.

Continuous quantitative data, such as pharma-
cokinetic model parameters, blood gas data, and re-
covery times, were assessed for normality by means
of Shapiro-Wilk tests. Normally distributed data were
analyzed by means of paired Student \( t \) tests that were
computed by comparisons of differences in the same
pharmacokinetic parameter or behavioral response
between anesthetic agents (sevoflurane or desflurane)
for each horse. Dobutamine doses needed to maintain
MAP between 70 and 80 mm Hg were summed over
the 5- and 40-minute periods immediately before and
after atipamezole administration. Dobutamine infu-
sion doses were analyzed by use of a 2-way repeated-
measures ANOVA that included agent (sevoflurane or
desflurane) and period (5 or 40 minutes before or after
atipamezole) in a full factorial model. Wilcoxon signed
rank tests were used to evaluate effects of an anes-
thetic agent on response measurements that were not
normally distributed or ordinal. Data were analyzed
with the aid of commercial statistical software.\(^7\) Values
of \( P < 0.05 \) were considered significant.

Results

Anesthetic induction and maintenance were
unremarkable in all horses. There was no significant
difference in blood pressures or blood gas tensions
between anesthesia maintained with desflurane and
sevoflurane. There was also no difference in dobuta-
mine requirements to maintain normotension in hors-
es anesthetized with either agent. The dobuta-
mine requirement was 40% and 16% higher for desflurane
and sevoflurane, respectively, during the 40-minute
period before atipamezole administration, compared
with the 40-minute period after atipamezole admin-
istration. However, during the 5 minutes immediately
before and after atipamezole administration, there was
no difference in the inotrope dose required to main-
tain normotension in horses anesthetized with either
agent.

During spontaneous ventilation immediately be-
fore disconnection of the breathing circuit and anes-
thetic recovery, mean \( \pm SD \) PacO\(_2\) was 56 \( \pm 6 \) mm Hg
and 64 \( \pm 8 \) mm Hg (\( P = 0.08 \)) and arterial blood pH
was 7.34 \( \pm 0.05 \) and 7.29 \( \pm 0.05 \) (\( P = 0.02 \)) for desflu-
rane and sevoflurane, respectively. Three minutes af-
ter disconnection of the breathing circuit, mean PaCO₂ was 47 ± 7 mm Hg and 58 ± 6 mm Hg (P = 0.02) and arterial blood pH was 7.38 ± 0.05 and 7.33 ± 0.04 (P = 0.02) for desflurane and sevoflurane, respectively. There was no significant difference in PaO₂ at the time of disconnection (P = 0.2) or at 3 minutes after disconnection (P = 0.5). Missing data caused by movement in many horses, particularly those receiving desflurane, precluded sample collection and meaningful comparisons of results for blood samples at later time points. End-tidal gas samples were collected for approximately the first 6 to 14 minutes of recovery after desflurane administration and for the first 10 to 17 minutes of recovery after sevoflurane administration. Representative anesthetic washout data and elimination pharmacokinetic models for both agents were determined (Figure 1). Summary statistics of pharmacokinetic models for all horses and both agents were calculated (Table 1). Neither the distribution slope and half-life nor the elimination slope and half-life were normally distributed, and none of these parameters differed significantly between inhalation agents. The AUC₀–∞ was nearly twice as large in horses during recovery after sevoflurane, compared with that during recovery after desflurane.

All horses recovered from both anesthetics without major injury; horses had a few small lip lacerations or abrasions for 3 of 12 recoveries. Objective recovery data and VAS scores were summarized (Table 2). There was very good interevaluator correlation (r² > 0.72; P < 0.001). No difference in overall subjective recovery quality was found between inhalation agents. Also, there was no significant difference between anesthetic treatments because horses had no or mild dysphoria (P = 0.1) and mild to moderate ataxia when standing (P = 0.8). However, most horses did not bang or slap their head against the floor of the recovery stall after desflurane administration, whereas this occurred significantly (P = 0.03) more often after sevoflurane administration. In addition, horses attained sternal recumbency and were able to stand significantly (P = 0.03) sooner after desflurane administration than after sevoflurane administration. Time to achieve sternal recumbency after desflurane administration explained approximately 64% of the variability in the amount of time for that same horse to achieve sternal recumbency after sevoflurane administration, although this correlation was not significant (P = 0.06).

**Discussion**

As predicted on the basis of the blood-gas partition coefficient of the anesthetic agents, horses in the present study recovered after desflurane administration much faster than after sevoflurane administration; there was a reduction in total recovery time of approximately 50%, which was equal to a mean difference of 20 minutes. This was reflected in the pharmacokinetic models by the reduction of approximately 50% in the AUC₀–∞ with desflurane, compared with results when sevoflurane was used, which can be interpreted to mean that each MAC fraction of desflurane was cleared more rapidly than that of sevoflurane. Again, this appeared to be primarily attributable to a median desflurane distribution constant that was > 50% larger, even though this difference was not significant because of the large sample variances. Additionally, sevoflurane is more soluble in oil and fat than is desflurane; thus, body tissues such as muscle, splanchnic organs, and especially adipose act as a reservoir that continues to accumulate anesthetic over time until the anesthetic partial pressure in a tissue is in equilibrium with the anesthetic partial pressure in arterial blood. During recovery, anesthetic released from these reservoirs redistributes to the vessel-rich tissue group that includes the CNS and opposes elimination from these sites of action. With increased body habitus or with increased anesthetic duration, more anesthetic can...
effects of inhalation anesthetics.\textsuperscript{25} All horses in the present study required dobutamine to support blood pressure prior to reversal of the $\alpha_2$-adrenoreceptor agonist. Mean dexametomidine half-life ranges from 20 to 29 minutes in awake young and aged ponies, respectively; and blood pressure, cardiac output, heart rate, stroke volume, and systemic vascular resistance normalize within 60 minutes after administration of doses similar to those used in the present study.\textsuperscript{14} Time-dependent decreases in the dobutamine requirement in the present study were most likely attributable to decreasing plasma concentrations of sedative and injectable drugs administered before inhalation anesthesia (such as dexametomidine) and to time-dependent increases in cardiac output that occur during constant-dose anesthesia.\textsuperscript{23} Lack of an immediate response to atipamezole after 1 hour of constant-

Table 1—Summary of pharmacokinetic parameters in 6 healthy adult horses during recovery from anesthesia maintained for 2 hours by administration of desflurane or sevoflurane at 1.2 MAC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
<th>$P$ value$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$ (mm$^{-1}$)</td>
<td>0.86 ± 0.09</td>
<td>0.68 ± 0.24</td>
<td>3.00</td>
</tr>
<tr>
<td>$\alpha$ (min$^{-1}$)</td>
<td>1.53 ± 0.94</td>
<td>0.90 ± 0.65</td>
<td>0.67</td>
</tr>
<tr>
<td>$B$ (mm$^{-1}$)</td>
<td>0.16 ± 0.09</td>
<td>0.33 ± 0.25</td>
<td>0.09</td>
</tr>
<tr>
<td>$\beta$ (min$^{-1}$)</td>
<td>0.69 ± 1.36</td>
<td>0.10 ± 0.06</td>
<td>0.95</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (min$^{-1}$)</td>
<td>2.18 ± 1.01</td>
<td>4.26 ± 0.87</td>
<td>0.69</td>
</tr>
<tr>
<td>$AUMC$ (min$^{-2}$)</td>
<td>22.14 ± 17.41</td>
<td>39.54 ± 17.04</td>
<td>0.67</td>
</tr>
<tr>
<td>$MRT$ (min)</td>
<td>9.02 ± 5.08</td>
<td>9.33 ± 3.91</td>
<td>0.57</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>0.79 ± 0.844</td>
<td>1.31 ± 1.05</td>
<td>0.99</td>
</tr>
<tr>
<td>$t_{1/3}$ (min)</td>
<td>7.67 ± 7.58</td>
<td>14.11 ± 18.65</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Horses were anesthetized with one of the inhalation agents; after a washout period of at least 1 week, horses then were anesthetized with the other inhalation agent. Anesthetic washout was characterized by use of the following equation for a 2-compartment model: $F_0 = Ae^{-t/\beta} + Be^{-t/\alpha}$, where $F_0$ is the end-tidal (estimating alveolar) concentration of anesthetic agent at various points during recovery, $F_0$ is the end-tidal concentration of anesthetic agent measured immediately before discontinuation of maintenance anesthesia, $A$ is the intercept of the semilogarithmic alveolar anesthetic fraction ratio versus time plot of the first (distribution) compartment, $e$ is the natural logarithm, $\alpha$ is the slope of the semilogarithmic alveolar anesthetic fraction ratio versus time plot of the first (distribution) compartment, $t$ is time, $B$ is the intercept of the semilogarithmic alveolar anesthetic fraction ratio versus time plot of the second (elimination) compartment, and $\beta$ is the slope of the semilogarithmic alveolar anesthetic fraction ratio versus time plot of the second (elimination) compartment.

\textsuperscript{a}Pharmacokinetic parameters were analyzed by means of paired $t$ tests (degrees of freedom = 5); values were considered significant at $P < 0.05$.

\textsuperscript{b}AUMC = Area under the first moment curve. MRT = Mean residence time. $t_{1/2a}$ = Distribution half-life. $t_{1/3}$ = Elimination half-life.

Table 2—Quantitative responses in 6 horses during recovery from anesthesia maintained for 2 hours by administration of desflurane or sevoflurane at 1.2 MAC.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
<th>$P$ value$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to sternal recumbency (min)</td>
<td>19 ± 7</td>
<td>33 ± 10</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to standing (min)</td>
<td>21 ± 8</td>
<td>41 ± 11</td>
<td>0.03</td>
</tr>
<tr>
<td>No. of attempts to achieve sternal recumbency</td>
<td>2 ± 2</td>
<td>5 ± 6</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of attempts to achieve standing</td>
<td>2 ± 1</td>
<td>2 ± 2</td>
<td>0.68</td>
</tr>
<tr>
<td>No. of head bangs or slaps against floor of recovery stall</td>
<td>1 ± 2</td>
<td>5 ± 6</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean VAS score (mm)$^+$</td>
<td>58 ± 30</td>
<td>58 ± 32</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Horses were anesthetized with one of the inhalation agents; after a washout period of at least 1 week, horses then were anesthetized with the other inhalation agent. Time represents the interval from disconnection of the anesthetic circuit until the specified event.

\textsuperscript{a}The VAS scores were analyzed by means of paired $t$ tests (degrees of freedom = 5), whereas all other responses were analyzed by means of Wilcoxon signed rank tests (degrees of freedom = 6); values were considered significant at $P < 0.05$. Two investigators who were unaware of the inhalation agent administered to each horse subjectively scored overall recovery quality on a 100-mm VAS.
dose anesthesia with an inhalation agent suggested that dexmedetomidine plasma concentrations were too low to appreciably affect blood pressure at that time point. Similarly, propofol is rapidly cleared,25 so the dose administered at anesthetic induction was unlikely to have affected cardiovascular function during the last hour of anesthetic maintenance. In contrast, guaifenesin is cleared much more slowly26 and was the injectable drug most likely responsible for increased vasodilation27 and persistent inotrope requirements in most horses during the final hour of anesthesia.

In the pharmacokinetic models, the distribution and elimination constants were numerically greater, but not significantly different, for desflurane, compared with the constants for sevoflurane. Given the significant difference in the blood-gas partition coefficient between agents,8 a larger and significant difference between washout curves would have been expected.28 There are 4 plausible explanations for why this was not observed. First, a difference might actually have existed but large intra-individual variability between agents increased sample variance that resulted in a false-negative error. Second, because of concerns about safety of personnel, collection of end-tidal gas samples ceased once a horse began lifting its head or moving its limbs during recovery. As a result, no samples were collected from horses at > 17 minutes of recovery. Results of computer simulations reveal that 3-compartment models describe tissue clearance of inhalation anesthetics better than do 2-compartment models.29 However, much longer washout times are needed to detect and characterize this third compartment than would be feasible for studies conducted with horses. Therefore, this unaccounted third compartment may have contributed to increased error or variability in the other 2-compartment parameters. Third, the blood-gas partition coefficient is a critical determinant of inhalation anesthetic pharmacokinetics, but it is not the sole determinant. Cardiac output or minute ventilation also affects alveolar anesthetic washout. Differences in cardiopulmonary responses, particularly differences in the degree of hypoventilation during the first few minutes of recovery (Table 1), to these agents may have obscured the effects of different agent blood-gas partition coefficients on elimination kinetics. Finally, 5% to 8% of sevoflurane undergoes hepatic metabolism, whereas ≤ 0.02% of desflurane is biodegraded.30 Metabolism decreases arterial and alveolar anesthetic partial pressures; hence, sevoflurane elimination kinetics was not entirely dependent on pulmonary alveolar washout.

Reports1,31 of horses anesthetized with sevoflurane or the more soluble haloether anesthetic isoflurane indicate that recovery quality is unaffected or improved when less soluble agents are used. Humans awake after 8 hours of desflurane anesthesia in half the time required following sevoflurane anesthesia of the same duration.32 Humans also have a greater sense of clearheadedness and more rapid return of coordination and mental faculties after desflurane-induced anesthesia,32 possibly because of less intertissue CNS redistribution during anesthetic washout of the less water- and fat-soluble desflurane, compared with the effects of sevoflurane.2 Horses in the present study also recovered much more quickly after desflurane administration than after sevoflurane administration, which might decrease complication risks from post-anesthetic myopathy and neuropathy. Recovery after desflurane also was characterized by less banging or slapping of a horse’s head on the floor of the recovery stall, which might be suggestive of greater clearheadedness in this species. However, all subjective evaluations of recovery quality did not differ between inhalation agents. Visual analogue scales and ordinal evaluation techniques yield results that are as reliable as those for other commonly used equine composite scoring systems,33 and evaluators in the study reported here had very good relative agreement between scores. It is possible that subjective scoring systems are simply insufficiently sensitive to detect modest differences in recovery quality characteristics that certain objective quantitative measures appear to suggest. Observations for the present study were made in the absence of postanesthetic sedatives. Although post-anesthetic sedatives increase the duration of recovery from anesthesia, they also increase the period for elimination of inhalation anesthetics and often improve recovery quality.34 Use of rapidly cleared sedatives or lower doses (or reversal) of longer-acting neuroleptic agents may make it possible to leverage the rapid elimination kinetics of desflurane to further improve recovery quality in horses. Studies are needed to test the validity of such a strategy.

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Footnotes
b. Suprane, Baxter Healthcare, Deerfield, Ill.
c. Dexdomitor, Zoetis, Florham Park, NJ.
d. US Compounding, Conway, Ark.
e. Diprivan, AstraZeneca, Wilmington, Del.
f. DateX-Ohmeda S/5 Compact, GE Healthcare, Fairfield, Conn.
g. Hospira, Lake Forest, Ill.
h. ABL800 Flex, Radiometer America, Westlake, Ohio.
i. Antiseden, Zoetis, Florham Park, NJ.
k. Clarus 500, PerkinElmer, Waltham, Mass.
l. TotalChrom, PerkinElmer, Waltham, Mass.
m. Life Assist Inc, Sacramento, Calif.

References
3. Wiese AJ, Broun RJ, Barter LS. Effects of acetycholinesterase


