Healthcare Corporation, Deerfield, Illinois: lot UR09D07248), which were stored at 5°C for 28 days with protection from light. Samples (5 mL each) collected on the day of preparation (day 0) and on days 7, 14, 21, and 28 days after preparation were transferred into clear glass test tubes. The samples were inspected for the presence of precipitate and any change in colour, and the pH was measured with a calibrated pH meter (Accumet 25, Fisher Scientific Inc, Nepean, Ontario).

To achieve the higher concentrations of bupivacaine (i.e., 20.0 and 37.5 mg/mL), a 4% solution, compounded in our Pharmacy Department, was used. The 4% solution is used in the hospital’s Pain Clinic for patients whose pain cannot be managed at lower concentrations.

All solutions packaged in either polypropylene syringes or non-DHEP bags remained clear and colourless throughout the course of the study. The pH of the solutions changed only slightly during the study, with a general trend toward becoming more acidic (Table 1).

Previous studies investigated the chemical stability and/or physical compatibility of various concentrations of bupivacaine and one of the narcotics at lower concentrations in minibags and found them to be stable for at least 72 h at various temperatures. The chemical stability and/or physical compatibility of the lower concentrations of mixtures stored in syringes was also studied; these mixtures were stable for at least 30 days at either room temperature or under refrigeration.

The compounded 4% solution of bupivacaine was needed to prepare the more concentrated solutions used in this study. Use of this solution might have caused a problem because the solution is at its saturation point for the drug at room temperature, and storage at 5°C might have caused precipitation. In this study, storage of solutions at 5°C represented a worst-case scenario. Barring future studies generating contrary information, mixtures stored at 5°C might have caused a problem because the solution is incompatible for 28 days when stored at 5°C with protection from light.

In conclusion, all solutions studied and packaged in either polypropylene syringes or non-DHEP bags were physically compatible for 28 days when stored at 5°C with protection from light.

References

Ronald F Donnelly, MSc(Chem), BSc(Pharm)
Keith Wong
Jennifer Spencer, BSc, BSc(Pharm), BCOP
Department of Pharmacy
The Ottawa Hospital
Ottawa, Ontario

At the time of the study, Keith Wong was a third-year student in the Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, and was working in the Pharmacy Department of The Ottawa Hospital as a summer student.

Are the Results of the RE-LY Trial Reliable?

Dabigatran is an oral thrombin inhibitor that is indicated in Canada for the prevention of venous thromboembolism in patients who have undergone hip or knee replacement. In the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapy), a 2-year multicentre non-inferiority trial, patients with atrial fibrillation who had an increased risk of stroke were randomly assigned (by allocation concealment) to receive dabigatran 110 mg twice daily or 150 mg twice daily (blinded) or warfarin (open-label). Concomitant use of acetylsalicylic acid (ASA, less than 100 mg/day) and amiodarone was allowed. In addition, use of quinidine was permitted until 2 years after the trial started; at that point, the protocol was amended to limit use of this drug because of its ability to increase plasma concentrations of dabigatran.

The authors of the RE-LY trial claimed that dabigatran was superior to warfarin at a dose of 150 mg twice daily with respect to preventing stroke and systemic embolism. In addition, both the 110-mg and 150-mg doses were reported to be superior to warfarin with respect to the rate of hemorrhagic stroke. However, we have been unable to confirm the authors’ conclusions because of flaws in the reported data and inadequacies in the reported components of the study.

The net clinical benefit (outcome) chosen for this trial, a composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, and major bleeding, encompasses problems typically seen with this class of medications, not those that are rare or yet to be discovered. Total serious adverse events were not reported, so the net effect of dabigatran cannot be assessed with certainty, especially given that there was a signal for increased risk of myocardial infarction relative to warfarin. Furthermore, although dabigatran 150 mg twice daily appears to be non-inferior to warfarin with respect to major bleeding, this dose of the drug is associated with a statistically significant increase in the risk of life-threatening or non-life-threatening gastrointestinal bleeding relative to warfarin. The choice of the patient population is questionable, given the authors’ report that nearly 6000 of the 18 113 patients in the study had a CHADS2 score of 0 or 1. CHADS2 is a risk stratification index describing the correlation between 5 known risk factors (congestive heart failure,
hypertension, age greater than 75 years, diabetes, and previous stroke) and the risk of stroke in patients with atrial fibrillation. The evidence to support treating patients with these CHADS(2) scores is controversial; generally, patients are treated with warfarin only if the CHADS(2) score is above 2. Patients with CHADS(2) scores below 2 could be considered for ASA therapy; as such, the RE-LY trial should have excluded patients with CHADS(2) score below 2 or should have considered an ASA arm.

The authors’ definition of systemic embolism did not detail if screening was mandatory for all patients or if the reported systemic emboli were from symptomatic or asymptomatic patients. Screening for asymptomatic events would increase the number of systemic emboli, regardless of their clinical relevance. It is also unclear from the data in Table 2 of the report the number of patients who had at least 1 systemic embolus, a fatal stroke, or fatal bleeding. Creatinine clearance was neither measured nor monitored during the study. Dabigatran is subject to primarily renal clearance (85%), and the degree of renal impairment is proportional to the extent of exposure to the drug. In patients with creatinine clearance below 30 mL/min, dabigatran is contraindicated, as plasma concentrations of the drug will be 6 times higher than in patients with normal renal function; in patients with creatinine clearance of 30–50 mL/min, concentrations will be 2.7 times higher. Therefore, patients in the dabigatran arms with moderate renal impairment could have experienced an increase in therapeutic effect or an increase in the risk of serious adverse events relative to patients in the warfarin arm.

Use of amiodarone, a drug that can increase plasma concentrations of dabigatran by 50%, was evenly distributed among the treatment groups; however, use of quinidine, a drug that is contraindicated for use with dabigatran because it can increase dabigatran concentrations by over 100%, was not noted in the baseline characteristics, and the distribution was not noted for each treatment arm. Once again, increased concentrations of dabigatran could have produced an increased therapeutic effect in terms of reducing coagulation but also increasing the risk for adverse effects. The selection of patients for the RE-LY study was done according to intention-to-treat principles; however, non-inferiority trials require a per-protocol analysis to confirm the non-inferiority that is observed with an intention-to-treat analysis. This had little impact in relation to the comparison between warfarin and dabigatran 150 mg and the finding of superiority; technically, a per-protocol analysis should have been part of the prespecified statistical plan.

We have contacted the corresponding author of the RE-LY study seeking clarification of these issues but have received no response to date. How RELY-able, then, are the claims made by the authors?

References

Matthew P Tsang, BSc(Pharm)
Aaron Tejani, BSc(Pharm), PharmD, ACPR
I fan Kuo, BSc(Pharm), ACPR, PharmD
Burnaby Hospital
Fraser Health Authority
Burnaby, British Columbia

Matthew Tsang was a Pharmacy Resident with the Fraser Health Authority in 2009/2010, when this letter was prepared.

---

**Advertisers’ Index**

<table>
<thead>
<tr>
<th>Ad Page</th>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>163-165</td>
</tr>
<tr>
<td>137</td>
<td>—</td>
</tr>
<tr>
<td>96</td>
<td>157, 158</td>
</tr>
<tr>
<td>IBC</td>
<td>171-175</td>
</tr>
<tr>
<td>103</td>
<td>166-170</td>
</tr>
<tr>
<td>IFC</td>
<td>—</td>
</tr>
<tr>
<td>OBC</td>
<td>—</td>
</tr>
<tr>
<td>99</td>
<td>159-162</td>
</tr>
</tbody>
</table>