PHARMACY PRACTICE

LEUCOVORIN TASTE CHALLENGE

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INTRODUCTION

Total Quality Improvement requires a constant search for ways in which to improve a system and reduce costs.[1] The Pharmacy Department at the Tom Baker Cancer Centre regularly reviews the drug inventory looking for interventions that can result in substantial cost savings. We would like to share our recent experience with leucovorin.

Leucovorin is available in both injectable and tablet formulations. Traditionally, the price per milligram of leucovorin has been approximately the same for each formulation. However, the recent entry of a generic leucovorin injectable formulation has resulted in a drop in the price. Catalogue prices indicate that, regardless of the supplier, the cost per milligram of the injectable leucovorin is approximately half that of the leucovorin in tablet form.

Pharmacists have often provided an injectable formulation of a drug for oral administration when no oral tablet or capsule is available (e.g., Mesna). Therefore, with cost minimization in mind, a calculation of the savings from administration of the less expensive injectable liquid compared to oral tablets was completed. This calculation considered the number of leucovorin oral rescue treatments, the cost of additional supplies to provide the liquid injectable leucovorin in an oral format, and the current drug acquisition cost for both the oral tablet and the injectable formulation. The cost analysis projected annual savings of $27,000 in our institution alone by switching from oral tablets to an oral liquid formulation of leucovorin. However, prior to a recommendation for conversion, issues of bioavailability, stability, palatability, and acceptability had to be addressed in an attempt to ensure equivalent patient outcomes.

Mehta et al[2] demonstrated that there was no significant difference in the concentrations of 5-methyltetrahydrofolate after either the liquid preparation prepared from the injectable or the more palatable tablet form of calcium leucovorin.

Selection of Diluents

Even if both formulations are bioequivalent, the salty taste of leucovorin must be masked effectively, otherwise patients would likely become non-compliant. Concern was raised by both nursing and pharmacy that since leucovorin is a rescue drug taken at home, noncompliance due to an unpleasant taste could lead to significant toxicities. Therefore, we investigated a suitable "diluent" that patients could use to mask this salty taste. This evaluation gave consideration to the pH dependency of leucovorin stability.

The pH of maximum stability for leucovorin is between 7.1 to 7.4, however, it shows good stability over the range of pH from 6.5 to 10[3] but degrades between a pH of 2.8 to 3.0.[4] The product monograph for calcium leucovorin injectable powder indicates that this formulation is stable for seven days at room temperature when reconstituted with bacteriostatic water for injection.[5] However, the newer injectable liquid formulation carries a much longer shelf life.[6] Therefore, provided that a diluent maintains a neutral pH or minimally a pH greater than 4, a chemically stable product would be predictable. Working with our dietary department, diluents were identified as theoretically preferred based on pH[4,7,8] (Table I). Using the diluents identified in Table I, a taste testing panel was formed using nursing and pharmacy staff.

METHODS

Nine different diluents listed in Table I were each tested by two different volunteers. Eighteen different volunteers participated in this taste panel - nine from nursing and nine from the pharmacy department. Each volunteer was asked to taste two 30 mL samples of the diluent of their choice identified only as Sample A or Sample B. Five mg of Leucovorin Calcium Injection (David Bull Laboratories) was added

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randomly to one of the four 30 mL samples of each diluent. The volunteers drank their Samples A and B in the order of their preference. After drinking both samples they were asked to complete the following questions:

Table I: Potential Diluents for Masking Leucovorin Taste

Recommendation Level[1]	pH Range	Diluent Examples
Preferred	6.5 - 6.7	dairy products, antacids, and meal replacements such as Ensure
Acceptable	> 4.0	tomato juice, prune juice, tea, coffee, cocoa, water
Least Preferred	3.6 - 3.8	club soda, apple juice, peach, pear and apricot nectar
Avoid	< 3.6	citrus fruit juices such as orange or grapefruit juice, most soft drinks such as Pepsi, 7-Up, gingerale, etc.

1. Although leucovorin shows good stability over the range of pH from 6.5 to 10[3], it degrades between a pH of 2.8 to 3.0[4]. Therefore, the recommendation level is based on an assumed stability advantage for diluents with a higher or neutral pH. Diluents with a pH less than 4.0 are not recommended.

Table II: Results of Taste Test

Diluent	Sample A	Sample B	Any taste difference ?	Better Tasting ?	Which Sample Contained Drug
white milk			no	–	–
white milk	drug		no	–	–
chocolate milk			no	–	–
chocolate milk	drug		no	–	A*
peach yogurt			no	–	A
peach yogurt	drug		no	–	–
tomato juice	drug		yes	A	B
tomato juice			yes	A	B
club soda	drug		yes	B	A+
club soda			no	–	–
chocolate mix with milk	drug		no	–	A*
chocolate mix with milk			no	–	–
black coffee	drug		no	–	A#
black coffee			no	–	–
Diovol antacid		drug	yes	A	B
Diovol antacid			no	–	–
chocolate Boost			no	–	–
chocolate Boost	drug		yes	A	B

* Subject could not identify a taste difference but could see milk in sample A was separating a bit.

\+ Subject thought club soda in sample A was flat, although it did not taste bad, but believed the leucovorin had flattened the soda.

\# Subject thought sample A smelled like sugar had been added. Therefore, although there was no taste difference, the leucovorin was identified as being in sample A.

1) Can you taste a difference between Sample A and B? 2) If yes, which sample tasted better? and 3) Which sample do you think contained leucovorin? Significance of differences in proportions were compared statistically using the Fisher Exact test and two tailed probability. The five percent level was selected *a priori* as the cut-off for statistical significance.

RESULTS

Results of the blind taste test are presented in Table II. Of the nine subjects that tasted a sample containing leucovorin, four detected a *difference in taste* compared to only one of nine control subjects. This difference is not significant ($p = 0.36$). However, only five of nine subjects receiving leucovorin samples were able to *correctly identify* the sample containing leucovorin, and in three of these subjects, leucovorin was identified by differences other than taste (Table II). This difference is also not statistically significant ($p = 0.30$). For both comparisons, as many as 34 subjects per group would have had to be tested to find statistical significance between these groups with proportions this different. Furthermore, of the four subjects that could detect a taste difference, two identified the leucovorin sample as better tasting. Therefore, the salty taste of leucovorin was not readily identifiable in a leucovorin containing sample.

DISCUSSION

This limited taste panel has demonstrated that the preferred diluents in Table I can effectively mask the taste of leucovorin. Patients now receive a bottle of oral leucovorin liquid, oral syringe, Adapta-cap, and a list of diluents they can choose to use with each dose. Patients receive instruction on the proper use of an oral syringe. Since the stability of leucovorin in any of these diluents has not been demonstrated, patients should

be instructed to mix leucovorin and a preferred diluent (Table I) immediately before use. To date no patient has required a switch back to tablets or to have pharmacy unit dose their oral liquid.

Before, during, and subsequent to this work-up, discussions were held at various committees within our facility and also provincially within the full Alberta Cancer Board organization. All stakeholders, including the pharmaceutical companies, were approached for input during this process. Support for this change was identified in both the physician and patient populations. Even prior to the completion of our taste panel, some physicians began to specify the diluent in which leucovorin should be mixed. However, by using pharmacy and nursing staff as taste panel subjects, front line personnel can now relate their tasting experience to patients and enhance patient compliance by suggesting diluents to mask the salty taste.

We conclude that switching from an oral tablet to an oral liquid formulation of leucovorin is feasible and can reduce leucovorin drug expenditures. Full implementation of this conversion has proceeded at our facility as well as provincially. Thus, the potential projected savings of $27,000/year at the Tom Baker Cancer Centre is proceeding and on track. Reviewing the pharmacy inventory and assessing alternate delivery systems should not be underestimated as a cost-saving measure in this time of restraint.

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