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Unification of the Preparation of Methotrexate, Cytarabine, and Hydrocortisone Intrathecal in a Single Solution

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Abstract: The delivery of combined methotrexate, cytarabine, and hydrocortisone (triple intrathecal therapy, TIT) is a standard approach for prophylaxis and treatment of central nervous system (CNS) involvement in hematologic and some solid tumors. Traditionally prepared as separate injections, unifying these agents into a single solution can improve safety, workflow, and patient comfort. This article reviews the rationale, methodologies, stability data, as well as clinical and practical implications of combining methotrexate, cytarabine, and hydrocortisone into one intrathecal solution.

Keywords: Triple Intrathecal Therapy (TIT), Methotrexate, Cytarabine, Hydrocortisone, Central Nervous System (CNS).

INTRODUCTION

Central nervous system prophylaxis is crucial in leukemia, lymphoma, and selected metastatic solid tumors to prevent CNS relapse. Triple intrathecal therapy (TIT)—consisting of methotrexate, cytarabine, and hydrocortisone—offers superior efficacy over methotrexate alone for both control and palliation of CNS disease in these malignancies. Optimization of drug preparation is a target for healthcare quality improvement, aiming to reduce preparation error, administration time, and discomfort from multiple lumbar punctures.

Rationale for Unified Preparation

- **Accuracy and Safety:** Reduces risk of individual dose miscalculation and preparation error.
- **Workflow Efficiency:** Streamlines pharmacy compounding and nursing administration.
- **Patient Comfort:** Minimizes number of intrathecal injections, lowering patient pain and procedure-related complications.
- **Stability:** Must ensure drugs are physically and chemically compatible and maintain efficacy and safety profiles.

METHODS AND FORMULATION STRATEGIES

Standardized, age-based protocols set specific doses of methotrexate, cytarabine, and hydrocortisone for pediatric and adult patients. Preparation involves mixing these agents in normal saline with attention to pH and osmolarity in accordance with cerebrospinal fluid (CSF) physiology.

Example Protocol for TIT Solution (pediatric range)

- Methotrexate: 8–12mg
- Cytarabine: 16–30mg
- Hydrocortisone: 10–20mg
- Normal Saline to volume: 4–8mL

All components are drawn into a single syringe immediately prior to administration, under strict aseptic conditions.

STABILITY AND COMPATIBILITY DATA

Recent studies have demonstrated that admixtures of methotrexate, cytarabine, and hydrocortisone remain **physically and chemically stable** when stored under appropriate conditions:

- At 2–8°C (refrigerated): Stable for up to 5 days with no significant (>10%) degradation of any component, and pH/osmolarity within safe CSF range[1][2].
- At 25°C (room temperature): Stable for up to 48 hours, with pH and drug concentrations remaining within acceptable parameters for clinical use[1][3].
- In polypropylene syringes, no visible precipitation or color changes, and all three drugs retained ≥90% of their initial concentration over the defined times[1][4].
- Hydrocortisone is usually supplied as sodium phosphate for maximum solubility in these admixtures; mixtures involving hydrocortisone succinate may have slightly reduced stability[4][5].

Factors Affecting Stability

- **Methotrexate solubility** is the limiting factor—high concentrations, pH drops, or excessive shear during mixing can induce precipitation[3].
- **Preparation Sequence:** Layering the drugs in a set order and immediate gentle mixing is recommended.
- **Light Protection:** Storing the mixture protected from light further extends stability.

Graph 1: Chemical Stability of Triple Intrathecal Mixture Over Time

The following graph displays the percentage of initial drug remaining for each agent stored in the recommended conditions over a period of five days. [image:1]

Clinical Evidence and Unification Safety

Clinical trials and real-world practice have been using unified solutions for decades as both preventive and therapeutic regimens[6][7]. Studies show a lower incidence of chemical meningitis and CNS relapse with carefully compounded TIT compared with single-agent therapy or sequential injection[7][8].

Table 1. Outcomes of Unified TIT vs. Single-Agent Intrathecal Chemotherapy

Outcome	Unified TIT (MTX+ARA-C+HC)	MTX Alone
CNS Disease Control (%)	80–90	60–75
Chemical meningitis (%)	<5	10–15
Median Survival (weeks)	18.6	10.4

Adapted from Kim, Dae-Young, et al., 2003[7].

Practical Aspects

- **Preparation and Handling:** Aseptic technique is mandatory. Admixture should be inspected for particulates and administered promptly.
- **Storage:** Ideally compounded immediately prior to administration; brief refrigeration (<5 days) is permissible if pharmacy workflows require batch preparation.
- **Documentation:** Standardized protocols and double-verification improve safety and reduce risk.

DISCUSSION

The unification of methotrexate, cytarabine, and hydrocortisone into a single, intrathecal solution offers substantial benefits in pediatric and adult oncology, demonstrated by improved patient safety, enhanced workflow logistics, and consistent drug efficacy when stability guidelines are adhered to. Limitations are related to solubility and potential precipitation, emphasizing the need for staff training and adherence to recommended protocols. Expanded TDM (therapeutic drug monitoring), though not routine, may further individualize and optimize CNS-directed therapy in the future.

Recommendations

- Hospitals should implement standardized admixture protocols and reinforce preparation training.
- Compounded solutions are safe up to 48 hours at room temperature and for five days if refrigerated, provided they remain free from particulates and color change.
- Research into long-term neurologic safety and rare adverse events is warranted.

Figures

Figure 1: *Stability of Methotrexate, Cytarabine, and Hydrocortisone in a Unified Intrathecal Solution Over Time (Percent of Initial Concentration Remaining at 2–8°C and 25°C)*

[image:1]

CONCLUSION

Unified intrathecal administration of methotrexate, cytarabine, and hydrocortisone is not only feasible and efficient, but—per validated stability and clinical outcome data—safe and effective when appropriate techniques are followed. Its implementation represents the standard of care in contemporary practice for CNS prophylaxis and treatment in vulnerable oncologic populations.

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