EVALUATING TOLERABILITY OF LONG TERM DIFLUNISAL THERAPY IN PATIENTS WITH TRANSTHYRETIN AMYLOIDOSIS

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Background

Diflunisal is an oral non-steroidal anti-inflammatory drug (NSAID) and transthyretin stabiliser, used for the treatment of transthyretin amyloidosis (ATTR). [1] Diflunisal prevents the release of amyloidogenic monomers which, in turn, reduces transthyretin formation and slows disease progression. [2] In patients with cardiac ATTR, therapy with diflunisal is associated with increased survival. [3]

The dose for amyloidosis is 250mg orally twice daily. [4] Presently, in Victoria, diflunisal is most commonly available as 500mg hard-coated tablets. This requires patients to halve the tablets, which is contrary to manufacturer's recommendations. Halving coated NSAID tablets could potentially further increase adverse effects and impact treatment tolerability. [5]

Objectives

Explore the tolerability of diflunisal in ATTR patients; and in particular evaluate the current approach of halving the hard-coated tablet formulation with respect to potential adverse effects.

Method

A retrospective review of ATTR patients dispensed diflunisal at Eastern Health between Nov 2014 - Dec 2022 was undertaken. This study received departmental ethical approval (QA19/056).

Results

125 patients were reviewed (refer to **Table 1** for patient demographic details). Diflunisal was discontinued in 67 (53.6%) patients (mean treatment duration of 18 months) **(Figure 1).** 98.4% of patients, were co-prescribed an acid-lowering agent at some point in time.

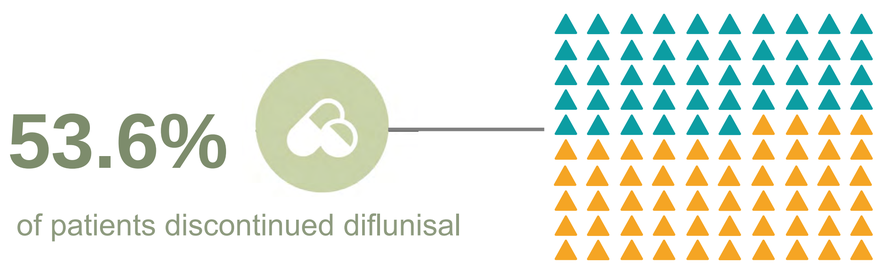
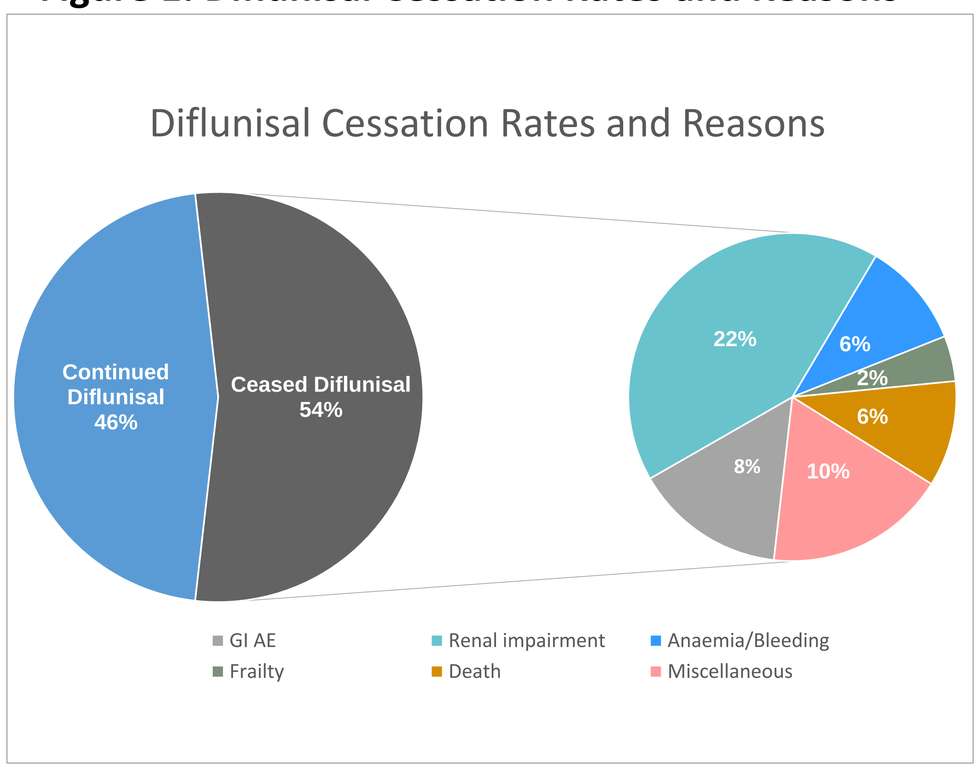


Table 1: Baseline Population Characteristics

Baseline Characteristics		n (%)	Median (Range)
Gender	Male	114 (91.2)	NA
	Female	11 (8.8)	
Age at diagnosis (yrs)	30-69	16 (12.8)	79 (30-92)
	70-79	57 (45.6)	
	80-100	52 (41.6)	
Mean treatment duration (months)	0-9	56 (44.8)	18 (0-92)
	10-29	38 (30.4)	
	30-59	23 (18.4)	
	60-99	8 (6.4)	
Gilmore Stage at diagnosis	1	85 (68.0)	NA
	2	29 (23.2)	
	3	9 (7.2)	

Figure 1: Diflunisal Cessation Rates and Reasons



Discussion

NSAID tablets, including diflunisal, are often coated to reduce GI side effects. For majority of products, including for diflunisal, the manufactures and practice guidelines do not recommend halving, crushing or modifying tablets in any way. [5] Provided the ongoing local practice of halving coated tablets at our centre, this study evaluated the rate of gastrointestinal adverse effects (GI AE).

8%

ceased diflunisal due to GI AE

This figure from our study is similar to data reported in other studies.

- **Ikram Et Al** evaluated safety and tolerability of diflunisal 250mg twice daily in 20 patients with transthyretin cardiac amyloidosis.
  - 3 patients (15%) ceased diflunsial due to GI AE. [6]
  - Median therapy duration:15 months
- **Berk Et Al** evaluated effect of diflunisal 250mg twice daily on polyneuropathy progression in patients with ATTR.
  - 23 out of 64 patients (35.9%) experienced GI discomfort; 1 patient (1.5%) discontinued diflunisal due to GI AE. [7]
  - Treatment duration: 2 years
- **Huskisson Et Al** compared tolerability and efficacy of diflunisal and aspirin as analgesics.
  - 967 patients in diflunisal group given either 250mg or 500mg twice daily for 5 days. Halving tablets not required.
  - 10.4% of patients in diflunisal group withdrew due to GI AE which is similar to our study. [8]
- This suggests halving tablets does not increase risk and severity of GI AE

Conclusion

Although practice guidelines recommend against halving diflunisal tablets, this study found that halving hard-coated diflunisal tablets did not increase the incidence or severity of GI AE when compared to the reported literature.

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